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Schaller, M.; Almeida, L.M.C.; Bewley, A.; Cribier, B.; Dlova, N.C.; Kautz, G.; ... ; Tan, J.

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M. Schaller,[1] L.M.C. Almeida,[2] A. Bewley,[3,4] B. Cribier,[5] N.C. Dlova,[6] G. Kautz,[7] M. Mannis,[8] H.H. Oon,[9] M. Rajagopalan,[10] M. Steinhoff,[11] D. Thiboutot,[12] P. Troielli,[13] G. Webster,[14] Y. Wu,[15] E. van Zuuren[16] and J. Tan[17]

[1]Department of Dermatology, Universitatsklinikum Tubingen, Tubingen, Baden-Württemberg, Germany
[2]Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, Brazil
[3]Whipps Cross University Hospital, London, U.K.
[4]Royal London Hospital, London, U.K.
[5]Department of Dermatology, Hopitaux Universitaires de Strasbourg, Strasbourg, Alsace, France
[6]Department of Dermatology, University of KwaZulu-Natal College of Health Sciences, Durban, South Africa
[7]Haut- und Laserklinik, Konz, Germany
[8]Department of Ophthalmology and Vision Science, University of California Davis, Davis, CA, U.S.A.
[9]National Skin Centre, Singapore
[10]Apollo Hospitals Enterprise, Chennai, Tamil Nadu, India
[11]Department of Dermatology and UCD Charles Institute for Translational Dermatology, University College Dublin, Dublin, Ireland
[12]Department of Dermatology, Pennsylvania State University College of Medicine, Hershey, PA, U.S.A.
[13]Faculty of Dermatology, Universidad de Buenos Aires, School of Medicine, Buenos Aires, Argentina
[14]Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, U.S.A.
[15]Department of Dermatology, Peking University First Hospital, Beijing, China
[16]Department of Dermatology, Leiden University Medical Centre, Leiden, the Netherlands
[17]Department of Medicine, University of Western Ontario, Windsor, ON, Canada

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Summary

Background Rosacea is currently treated according to subtypes. As this does not adequately address the spectrum of clinical presentation (phenotypes), it has implications for patient management. The ROSacea COnsensus panel was established to address this issue.
Objectives To incorporate current best treatment evidence with clinical experience from an international expert panel and establish consensus to improve outcomes for patients with rosacea.
Methods Seventeen dermatologists and three ophthalmologists reached consensus on critical aspects of rosacea treatment and management using a modified Delphi approach. The panel voted on statements using the responses 'strongly disagree', 'disagree', 'agree' or 'strongly agree'. Consensus was defined as ≥ 75% 'agree' or 'strongly agree'. All voting was electronic and blinded.
Results The panel agreed on phenotype-based treatments for signs and symptoms presenting in individuals with rosacea. First-line treatments were identified for individual major features of transient and persistent erythema, inflammatory papules/pustules, telangiectasia and phyma, underpinned by general skincare measures. Multiple features in an individual patient can be simultaneously treated with multiple agents. If treatment is inadequate given appropriate duration, another first-line option or the addition of another first-line agent should be considered. Maintenance treatment depends on treatment modality and patient preferences. Ophthalmological referral for all but the mildest ocular features should be considered. Lid hygiene and artificial tears in addition to medications are used to treat ocular rosacea.
Conclusions Rosacea diagnosis and treatment should be based on clinical presentation. Consensus was achieved to support this approach for rosacea treatment strategies.

Correspondence
Martin Schaller.
E-mail: martin.schaller@med.uni-tuebingen.de

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Conflicts of interest
See Appendix.

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What's already known about this topic?

- The current subtype-led rosacea diagnosis/classification system does not adequately cover the spectrum of clinical presentation and has implications for patient management.
- High-quality controlled trials for rosacea interventions are increasing, but there are still gaps in the evidence and the recommendations in existing guidance are disparate.
- Currently there is no phenotype-based approach to rosacea management.

What does this study add?

- This international expert panel proposes a phenotype-led approach to rosacea management that addresses individual rosacea features. It incorporates best evidence, clinical experience and recent developments in the management of patients with rosacea.
- This article provides current ophthalmological expert perspectives on ocular rosacea for a dermatologist audience.
- This article also describes an approach to combination treatment and maintenance therapy of cutaneous rosacea features.

Rosacea is a chronic inflammatory skin disease without a universally accepted definition[1] or confirmed pathophysiology.[2,3] Its prevalent subtype-led diagnosis and classification system is associated with a number of issues, which has prompted the proposal to transition to a phenotype-led approach (discussed in depth elsewhere).[4] The discord between subtypes and phenotypes is relevant here because it has implications for both clinical practice and research. Treatment based on presenting features rather than subtypes could improve patient outcomes, by targeting those aspects most bothersome to the patient. Furthermore, given the overlap of rosacea features across subtypes and the fact that no single treatment completely addresses all rosacea features,[5] it is likely that multiple treatments will be needed to address the spectrum of features in an individual patient.[1]

Many clinical trials in rosacea recruit patients using subtype-based inclusion criteria and assess treatment outcomes according to those subtypes. As a result, treatment progress may be hindered because the full spectrum of presenting features may not be addressed. The overall prevalence of well-powered, well-conducted randomized controlled trials (RCTs) in rosacea is increasing, but evidence is still sparse in a number of areas, with variable assessment methodologies that could be of higher quality in many clinical trials.[1,6] Furthermore, less common presentations, such as phymatous changes and ocular rosacea, receive less attention than the more common features such as inflammatory papules/pustules and erythema. This is exemplified in a 2015 Cochrane review on interventions for rosacea, which found no eligible RCTs for patients with phymatous changes and few for ocular rosacea.[1]

The same Cochrane review summarizes available evidence for rosacea treatments by accounting for treatment efficacy and risks shown in clinical trials.[1] The review used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence,[1] which is a patient-centred approach.[7] As only RCTs are included in the Cochrane review, it does not account for clinical experience or data from other study designs such as observational studies and case series.[1] Therefore, this review is unable to address adequately the less common features of rosacea for which no RCTs exist and it omits studies published after the proximate time range of the literature search.[1] Where RCT evidence is lacking for particular treatments or features, a consolidated body of clinical evidence including the clinical experience of experts may support treatment decisions.

Recent advances in the understanding of rosacea pathogenesis, as well as trials that have specifically addressed a single feature instead of a subtype, have prompted developments in treatment options.[8] This is a positive step towards treating rosacea according to its phenotypes, rather than subtypes; accordingly, local groups have recently progressed to phenotype-based treatment recommendations.[9] However, no guidance from a global perspective exists for this approach for treating rosacea, and consensus is still needed to support this new approach. This consensus document from the international ROSacea COnsensus (ROSCO) panel incorporates current best evidence as per the 2015 Cochrane review on interventions for rosacea,[1] which includes clinical experience from an international expert panel, with the aim of establishing a truly global consensus to improve outcomes for patients with rosacea.

Materials and methods

The ROSCO international panel consisted of 17 dermatologists and three ophthalmologists and used a modified Delphi process, consisting of e-surveys and a group meeting, to reach consensus (methods have been reported previously[4] and are detailed in the Supporting Information. Table S1; see Supporting Information).

Relevance of outcomes

The ROSCO panel incorporated GRADE quality of evidence from the Cochrane review on interventions for rosacea into their discussion on rosacea treatments in order to combine available evidence with clinical experience in the consensus statements. The Cochrane review used the GRADE approach to rate the quality of evidence from the studies assessed as high, moderate, low or very low.[1] The strength of a recommendation in GRADE reflects the confidence that the desirable effects of an intervention outweigh the undesirable effects.[10] Considerations may include factors such as morbidity and mortality, quality-of-life improvement, changes in treatment burden, adverse effects and changes in the use of resources. GRADE recommendations have two strengths, i.e. strong and weak.[10]

Consensus statements required advisors to rate their level of agreement as 'strongly disagree', 'disagree', 'agree' or 'strongly agree'. Consensus was reached if $\geq 75\%$ voted 'agree' or 'strongly agree'. Some questions were open-ended to allow for the development of consensus statements in a subsequent round of voting. Consensus is denoted in quotation marks and voting scores in brackets (e.g. 15 of 17; 15 of 17 voted 'agree' or 'strongly agree'). The strength of the recommendation is indicated by the wording of the consensus statements. For example, '*x* was agreed' is a higher degree of consensus than '*x* was considered'. Elements that were discussed but not voted on are also included below.

Results

Full consensus statements and voting results are included in the Supporting Information (Table S1; see Supporting Information).

Cutaneous features

General skincare

The majority of panellists (15 of 18) agreed that the education and instruction of proper general skincare is essential for all patients with rosacea in order to ensure the best possible treatment outcomes. Essential skincare advice elements include the use of sunscreen (sun protection factor 30+) (17 of 18), frequent use of moisturizers (15 of 18), use of gentle over-the-counter cleansers (16 of 18) and known trigger avoidance (18 of 18). General skincare was agreed to be the main management strategy for the secondary features of rosacea, which included dry appearance, dry sensation and stinging sensation (12 of 15).

First-line treatment

Table 1 shows a phenotype-led treatment algorithm drawn from the consensus statements relating to major cutaneous features, i.e. transient erythema, persistent erythema, inflammatory papules/pustules, telangiectasia and phyma. The treatments listed in the table are considered first-choice options for the treatment of each rosacea feature. The panel considered each feature and its severity individually and based decisions

Table 1 A phenotype-led treatment algorithm for the cutaneous features of rosacea, based on consensus statements from the ROSacea COnsensus panel

		Inflammatory papules/pustules				Phyma	
Transient erythema[a]	Persistent erythema[b]	Mild	Moderate	Severe	Telangiectasia	Clinically inflamed	Clinically noninflamed
α-adrenergics (topical)	Brimonidine (topical)	Azelaic acid (topical)	Azelaic acid (topical)	Ivermectin (topical)	Electrodessication	Doxycycline (oral)[c]	Physical modalities
Beta blockers (oral)	IPL	Ivermectin (topical)	Ivermectin (topical)	Doxycycline (oral)[c]	IPL		
	PDL	Metronidazole (topical)	Metronidazole (topical)	Isotretinoin (oral)	Lasers		
		Doxycycline (oral)[c]	Doxycycline (oral)[c]			Isotretinoin (oral)	
General skincare (sun protection factor 30+, moisturizers, gentle cleansers, trigger avoidance).							

Not all products or indications are licensed in every country and may be subject to further local variations. For specific product information the local label should always be consulted. Doxy, doxycycline; IPL intense pulsed light; PDL, pulsed-dye laser. [a]There is no high-quality evidence for flushing treatments; consensus on this statement is based on case reports and clinical evidence. [b]Persistent centrofacial erythema associated with periodic intensification by potential trigger factors. [c]Doxycycline 40 mg superior to placebo; doxycycline 40 mg noninferior to doxycycline 100 mg. No inference possible from indirect comparison.

on available evidence and clinical experience. There was agreement that treatment for inflammatory papules/pustules should vary by severity. For phyma, treatment should depend on whether it is clinically inflamed ('active') or clinically noninflamed ('fibrotic' or 'burnt out').

Combination therapy

The panel agreed that multiple cutaneous features of rosacea can be treated with more than one agent simultaneously (15 of 15). There was consensus that if first-line treatment fails, physicians should either consider an alternative first-line option as depicted in Table 1, or add an additional first-line agent (16 of 17).

There was agreement that moderate and severe presentations of major features require a combination of treatments, which could include general skincare or physical modalities as well as pharmaceutical agents. The exception was telangiectasia, for which opinion was divided over the use of monotherapy or combination therapy at any severity level. Opinion was also divided on whether mild presentations should be treated with monotherapy or combination therapy.

Maintenance therapy

The panel was in unanimous agreement (17 of 17) that the approach to rosacea maintenance therapy depends on treatment modality and patient desire for ongoing therapy. The minimum treatment to maintain control should be used. Additionally, treatments should be used for sufficient duration before switching to an alternative. The definition of 'sufficient duration' is specific to the treatment.

Ocular features

The purpose of this section is to indicate the current opinion among ophthalmologists who are experts in ocular rosacea, where at least two of three panellists agreed on a statement, as ocular rosacea is considered to be a multidisciplinary challenge.[11] As only three ophthalmologists were involved in the ROSCO project, the ocular rosacea outcomes may be less generalizable than those relating to cutaneous features.

The ophthalmologists would not expect referral from a dermatologist in the cases of very mild ocular rosacea that do not bother the patient. For greater severity, which cannot be controlled with lid hygiene, referral to an ophthalmologist should be considered. Despite expecting a dermatologist to recognize blepharitis, blurred vision, foreign body sensation, interpalpebral bulbar hyperaemia, photophobia, redness, tearing and telangiectasia as ocular rosacea features, the ophthalmologists would not expect treatment prior to referral, with the exception of prescribing artificial tear substitutes for mild ocular burning/stinging.

Important general eye care factors for managing ocular rosacea are ultraviolet-coated sunglasses and lid hygiene. Proper instruction/teaching of general eye care can ensure the best possible treatment outcomes. Optimal lid hygiene consists of warm compresses, meibomian gland expression, dilute baby shampoo scrubs and lubricating drops.

Table 2 shows the treatments used for ocular rosacea by severity level. The ophthalmologists considered ocular treatments, particularly topical medications, to have additive effects. When treating patients who have ocular rosacea in addition to other cutaneous features, the ideal scenario is to treat the ocular rosacea and cutaneous features with an optimized combination of therapies targeted for the presenting features.

Discussion

The ROSCO panel achieved consensus on initial, combination and maintenance therapy relating to a phenotype-led approach for treating cutaneous rosacea features. These have been developed into an algorithm for first-line therapy, detailing treatments by individual major features, i.e. transient erythema, persistent erythema, inflammatory papules/pustules, telangiectasia and phyma. The ophthalmologists also provided an approach to ocular rosacea management.

The treatment algorithm is accompanied by guidance on combination and maintenance treatment approaches, to aid physicians in adjusting or combining treatments depending on the patient's rosacea phenotype and response to therapy. The ROSCO panel agreed that the two phenotypical presentations diagnostic of rosacea in the absence of other features are

Table 2 Treatment options for ocular rosacea by severity level

	Mild (mild blepharitis with lid margin telangiectasia)	Moderate (blepharoconjunctivitis/ blepharokeratoconjunctivitis)	Severe (sclerokeratitis)
Topical	Lid hygiene	Lid hygiene and ciclosporin	Lid hygiene and topical corticosteroids
Systemic[a]	Dietary supplementation Doxycycline 40 mg MR	Doxycycline 40 mg MR	Doxycycline 40 mg MR Doxycycline ≥ 50 mg

Multiple treatments may be used simultaneously, e.g. a topical and a systemic agent. Note that ocular signs/symptoms may present with or without skin disease. MR, modified release. [a]May not be necessary for some mild cases.

phymatous changes and persistent erythema associated with periodic intensification by potential trigger factors. Other rosacea features must appear in combination in order to be considered diagnostic (data published separately).[4] Therefore, parallel combination therapy is likely to be a required aspect of a phenotype-led approach to rosacea management. It has previously been suggested that physicians should choose a combination of treatments based on disease activity, severity and presenting features.[1,5,11–13] However, guidance on the use of multiple rosacea treatments in combination should be more dependent on the individual patient's expression of concern and desire for treatment.[1]

General skincare and eye care underlie the treatment approach to managing cutaneous and ocular features, respectively. The Cochrane review on interventions for rosacea found a lack of RCTs for patient education and trigger factor avoidance, and failed to identify any eligible studies addressing dietary manipulation or sun-protective measures; however, the review stated this was an important area for further research.[1] Other groups stress the importance of appropriate skincare and education as significant partners to medical treatments for rosacea.[5,11,12,14–16] Therefore, general skincare and eye care are likely to feature as a component of combination therapy. Dietary supplementation also featured as a treatment option for ocular symptoms of rosacea, specifically, increasing the ratio of omega-3 to omega-6 fatty acids from natural sources such as coldwater fish and flaxseed oil, which downregulates inflammatory processes in the body.[17] These interventions require further investigation.[1]

Evidence for treating transient erythema in rosacea is limited, which has resulted in no formal treatment recommendations from other groups.[9] Based on clinical experience and case reports, the ROSCO panel felt that topical α-adrenergics and oral beta blockers are viable treatment options. A specific mention was given to brimonidine in the topical α-adrenergic class and carvedilol in the oral beta blocker class.

Oral doxycycline, a tetracycline antibiotic, featured as a treatment that could be considered for all severities of inflammatory papules/pustules, clinically inflamed phyma and ocular features of rosacea. Dosage is not specified, owing to the availability of several formulations globally. In addition to the standard formulations of ≥ 50 mg, which have antibiotic activity, doxycycline is also available in some regions as a 40-mg modified-release (MR) dose, which is considered to have anti-inflammatory but not antibiotic activity, and reduced gastrointestinal side-effects vs. doses ≥ 50 mg.[18] The latter is considered by the ROSCO panel to be a viable treatment option in regions where it is available, which may alleviate concerns over antibiotic resistance.[18–22]

Many physicians use other tetracycline antibiotics to treat inflammatory papules/pustules of rosacea, with moderate quality of evidence reported regarding their efficacy.[1] Although the panel reached consensus not to include tetracyclines as a class in the algorithm for first-choice therapy, some authors felt strongly that this should still be an option in situations where doxycycline is unsuitable or unavailable.

Patient values and preference should play a role when choosing between treatment options. In particular, it should be a major factor in the decision between laser vs. topical therapy for clinically inflamed phyma, and in laser vs. nonlaser physical modalities for clinically noninflamed phyma. Nonlaser physical modalities could include surgery and microdermabrasion. The panellists felt that it was important to divide phyma into clinically inflamed and noninflamed, as treatment options would differ accordingly.

A patient's comorbid conditions may also affect medication choice. For example, rosacea is associated with migraine[23] and gastrointestinal disorders.[24] Oral beta blockers are considered an effective migraine prophylactic and recommended by several groups,[25–28] which could be a consideration when treating transient erythema of rosacea with comorbid migraine. Similarly, agents such as antibiotics that are associated with increased gastrointestinal side-effects may be less appropriate to treat rosacea features in a patient with gastrointestinal comorbidities.

Treatment should be allowed sufficient time to take effect before considering it a failure and choosing another option. However, the evidence around 'sufficient time' is variable. Previous suggestions around duration of initial therapy range from 6 to 12 weeks, depending on whether the agent is topical (shorter duration) or oral (longer duration), and should be tailored to the patient.[12,16] The Cochrane review found that study duration was < 8 weeks in 32 of the 106 studies included, which the authors considered inadequate to demonstrate the efficacy of many interventions.[1] The review concluded that more studies are required to assess remission maintenance, time needed to response and response duration.[1]

As a chronic condition with periodic remissions and relapses,[5,12] long-term management is likely to require adjustments to therapy over time in order to maintain control. The ROSCO panel consensus on long-term treatment is a flexible one that depends on the treatment and the patient's requirements. Overall, existing guidance on the long-term management of rosacea is limited, with a focus on topical treatments rather than systemic therapy and time frames of months rather than years.[1,11,16] Several panellists proposed the investigation of basal anti-inflammatory agents in maintenance treatment as this is a well-established approach for many other chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease.[29,30] Several existing rosacea treatments, including metronidazole and doxycycline 40 mg MR, appear to target the inflammatory cascades involved in the pathophysiology of some rosacea features; however, further research is required in this area.[31]

The Delphi process is increasingly used to develop treatment guidelines and recommendations, owing to its systematic, egalitarian approach and scope for qualitative evidence assessment.[32–38] Some researchers have expressed concerns over bias, reproducibility, and that this approach is not necessarily 'evidence based' because existing evidence may contradict the panellists' collective opinion.[32,38] However, owing to its exploratory nature, the Delphi process is not recommended

for reaching consensus in areas with plentiful evidence or where the subject is already clear-cut.[39] By contrast, in cases such as that addressed in the present article, where the issues specifically relate to expert experience and opinion because of a lack of evidence in the area, the Delphi process is well suited.[39]

The panel attempted to overcome any concerns over bias in the Delphi process through blinded voting and by combining evidence from the Cochrane review with clinical expertise, as a means of incorporating the evidence most appropriate for addressing the question at hand. Cochrane reviews consider RCTs the best study type for assessing the efficacy of a treatment or intervention[40] and, hence, the Cochrane review included only RCTs while excluding other study designs.[1] Given the dearth of RCTs for certain rosacea features and treatments,[1] the panel also considered the wider body of evidence in the form of a summarized literature review, the process and content of which have been described elswhere.[4] As a result, ROSCO recommendations also include less common features such as phyma and ocular rosacea.

ROSCO is the sole international panel of dermatologists and ophthalmologists to develop consensus recommendations for rosacea treatment. It has built on existing systematic reviews of evidence and incorporated clinical experience, to propose a globally applicable treatment algorithm based on phenotype. These recommendations provide a basis for adaptation and development of local clinical practice guidelines, considering access factors such as treatment availability, patient values/preferences and cost.

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Appendix

All panellists received honoraria from Galderma for participating in this meeting. A.B., N.C.D., G.K., M.M. and Y.W. have no further conflicts of interest to disclose. M.Sc. was a member of the Galderma and Marpinion advisory board during the past 2 years and has received lecture fees from AbbVie, Bayer Healthcare, Galderma, and La Roche-Posay. L.M.C.A. has served as a speaker and advisory board member for Bayer, Galderma and Glenmark, and as a researcher for Galderma. B.C. has served as a speaker and board member for Galderma, and speaker for Avène and La Roche-Posay. H.H.O. has served as a speaker, advisory board member and researcher for Galderma. H.H.O. is also a clinical investigator for Janssen, Novartis and Pfizer and an advisory board member for AbbVie. M.R. has been an advisory board member for Novartis, Janssen, Wyeth, Pfizer, Biocon, Dr Reddy's Laboratories, Sun Pharma and UCB. M.St. has been an advisor to Almirall, AbbVie, BMS, Galderma, GSK, Pierre Fabre, Pfizer and Sanofi. M.St. has also been a consultant to Galderma, Sol-Gel, Sanofi and Pfizer, a clinical investigator for Almirall, BMS, Pierre Fabre, Galderma and Pfizer, and a speaker for Galderma, Novartis, Toray, Maruho. D.T. has been a consultant to Dermira, Galderma, Novan, Cassiopea, Mimetica, Sebacia and an investigator for Galderma, Novan, Mimetica, Sebacia, Merz, Cassiopea and Allergan. P.T. has served as speaker, consultant and clinical investigator for Galderma and La Roche-Posay, and has been advisory board member to AbbVie and Novartis. G.W. is a consultant to Galderma, Foamix, Sol-Gel, Dermira, Valeant, Cipher, GSK, Vitae, Aclaris, Alexar, Sienna, Janssen and Johnson & Johnson. E.v.Z. has served as a speaker for Galderma. J.T. has been an advisor and/or speaker for Almirall, Bayer, Cipher, Galderma, Stiefel/GSK, Merz and Valeant. J.T. is also a consultant to Galderma, Merz, Roche and clinical investigator for Allergan, Cipher, Dermira and Galderma.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Consensus statements and results.

Video S1. Author video.