doi:10.36849/JDD.M0922

 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Skin Barrier Deficiency in Rosacea: An Algorithm Integrating OTC Skincare Products Into Treatment Regimens

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ABSTRACT

Introduction: Rosacea is a chronic condition involving inflammation leading to a diminished skin barrier function in sebaceous gland-rich facial skin. The current algorithm represents part II of a series investigating similar topics associated with preventing, treating, and maintaining rosacea, including ceramides-containing skincare.

Methods: The consensus process consisted of a modified Delphi technique. A previously published review by the US Cutaneous Rosacea Outcomes (USCRO) group on skin barrier deficiency in rosacea and the integration of over-the-counter (OTC) products and skincare recommended for rosacea treatment and maintenance informed the development of the current algorithm. The selected information from the literature searches, coupled with the USCRO group's opinion and experience, was used to develop, discuss, and reach a consensus on an evidence-based clinical treatment and maintenance algorithm focusing on rosacea phenotypes.

Results: The algorithm includes foundational measures to be taken by all patients with rosacea and rosacea-prone skin. These measures include education, behavioral modifications, avoidance of triggers and skin irritants, preventative skincare, and sun avoidance and sunscreen use. The algorithm further describes how assessment of skin condition and grading of cutaneous rosacea should take place during treatment and maintenance while the preventative measures continue.

Conclusions: Prescription medications combined with gentle cleansers, moisturizers, and sunscreen support a successful rosacea therapy.

J Drugs Dermatol. 2022;21:9(Suppl 1):s3-10.

INTRODUCTION

Rosacea is a common relapsing facial skin condition most prevalent in Caucasian women from the Northern hemisphere, although this is likely due to reporting bias.[1,2] Historically, rosacea has been considered uncommon in richly pigmented skin, but recent reports highlight rosacea in other skin phototypes including in Asian and African populations.[2,3]

Genetic factors play a clear but ill-defined role in the development of rosacea.[2,3]

Rosacea's pathophysiology is not entirely understood. However, dysregulation of the immune system and nervous and vascular systems changes have been identified.[1,3,4] Rosacea is characterized by inflammation and vasculopathy and presents with pruritus, burn, and sting symptoms and an increased incidence of irritant and allergic contact dermatitis.[1,4-6] Chronic inflammation leads to a diminished skin barrier function in sebaceous gland-rich facial skin affected by rosacea.[7-9] Clinical studies in rosacea patients have shown increased transepidermal water loss (TEWL), reduced skin hydration, elevated skin surface pH, and increased lactic acid stinger reaction indicating skin barrier deficiency in rosacea.[6,10-16] However, specific lipid abnormalities in rosacea-prone skin

have not yet been studied.[6] Moreover, disruption of the healthy skin microbiome may be of pathological significance.[16-20] The resulting dysbiosis could be a pathological driver of rosacea or a response to changes in the skin microenvironment resulting from rosacea.[16-20]

Skin barrier dysfunction is addressed by using skincare, including gentle cleansers and moisturizers, recommended before and during prescription therapy and for maintenance improvement.[6] To maximize rosacea patient outcomes, an expert panel of dermatologists (advisors) who treat patients with rosacea developed a clinical treatment and maintenance algorithm focusing on the use of over-the-counter (OTC) products, skincare, and sun protection.

The US Cutaneous Rosacea Outcomes (USCRO) Project

The current algorithm represents part II of a series investigating similar topics associated with the prevention, treatment, and maintenance of rosacea.[6] A previously published review by the USCRO (US Cutaneous Rosacea Outcomes) group on skin barrier deficiency in rosacea and the integration of OTC products and skincare recommended for rosacea treatment and maintenance informed the development of the current algorithm.[6] The USCRO advisors' publication included the results of a literature review and a survey coupled with the advisor's expert opinion and experience.[6] The advisors agreed OTC products and skincare play an important role in improving skin barrier function and rosacea symptomatology.[6] However, further exploration of clinical aspects of OTC product use and their specific ingredients of interest is required to integrate this knowledge into the current algorithm.[6]

SCOPE

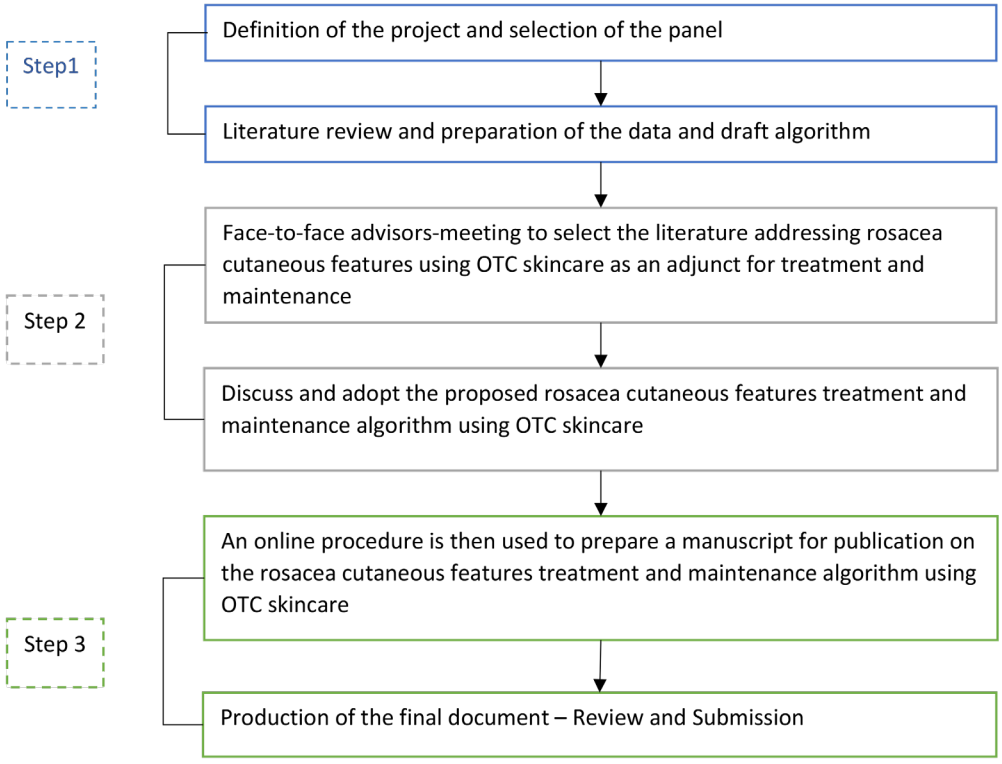
The same group of dermatologists who previously published the USCRO review paper[6], developed, discussed, and reached a consensus on an evidence-based clinical treatment and maintenance algorithm focusing on rosacea phenotypes.

The foundational measures for all rosacea patients during treatment and maintenance include behavioral modification, OTC skin care measures, and skincare regimens including hygiene, moisturization, and sun protection measures and products.[6] The USCRO algorithm aims to improve patient outcomes and determine the best approach for all US healthcare stakeholders' rosacea treatment and maintenance programs.

MATERIALS AND METHODS

The process entailed preparing the project, selecting the advisors, conducting systematic literature searches, summarizing the literature search results, grading the literature, and drafting the algorithm. The advisors used a modified Delphi approach following the AGREE II instrument in the algorithm's development.[21,22] The modified Delphi method is a communication technique for medical project interactive decision-making.[22] The process was adapted from face-to-face meetings to a hybrid model. The face-to-face discussion was followed by an online follow-up, replacing a questionnaire.[22]

FIGURE 1. The process.



On October 30, 2021, the advisors convened a face-to-face meeting to discuss the outcome of literature searches and reach a consensus on the algorithm based on the selected literature.[21,22] During the meeting, the advisors reviewed the systematic literature review results and discussed and adopted the algorithm using evidence coupled with their expert opinion and experience. A further online process was to fine-tune the algorithm, reach a consensus and prepare and review the publication (Figure 1). The advisors' consensus on the algorithm was established as an eighty-five percent (6/7) agreement was obtained.

Literature Review

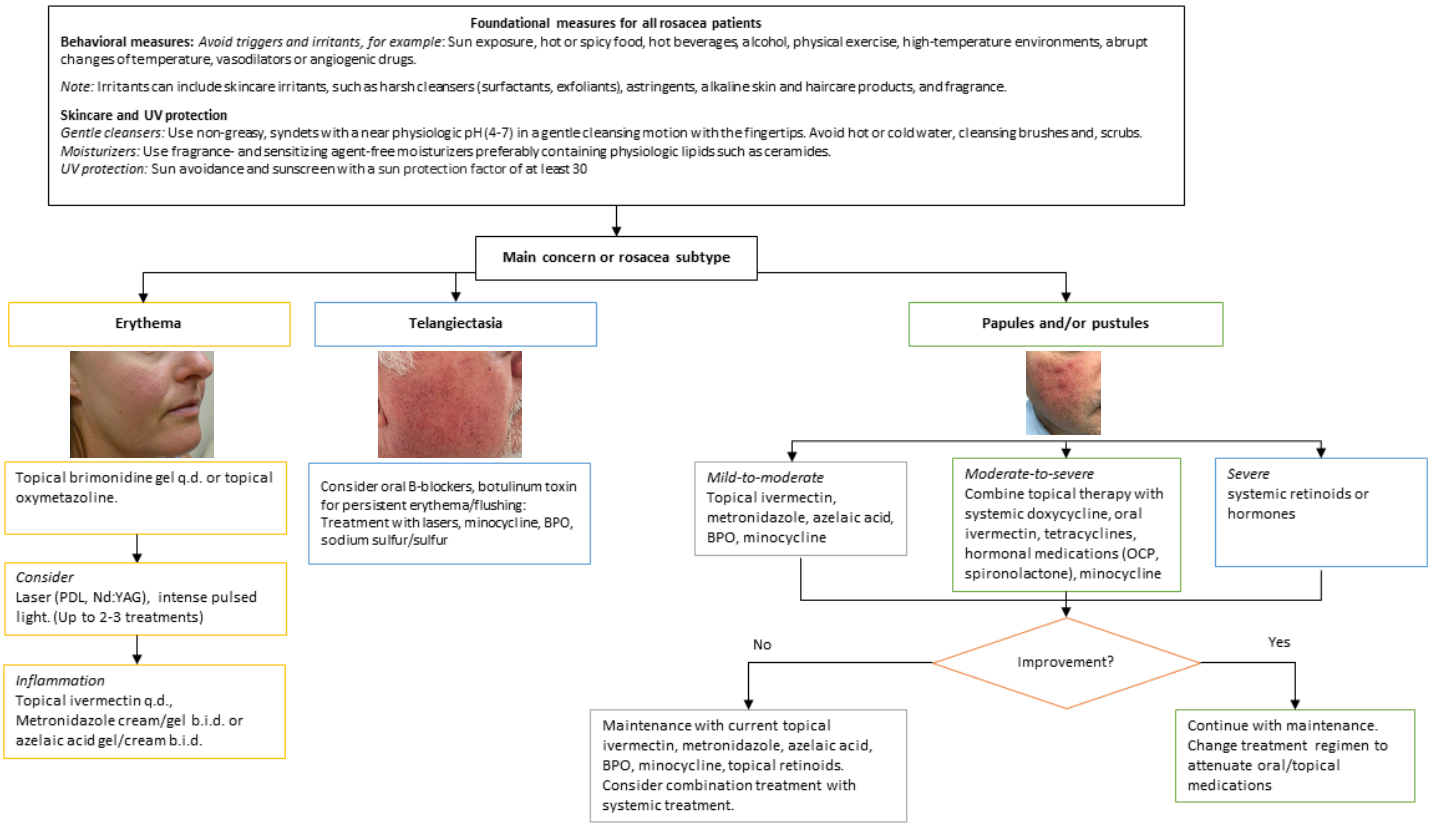
A literature review included guidelines, consensus papers, and publications describing current best-practice in rosacea and skin barrier dysfunction features to inform the development of a clinical algorithm for rosacea treatment and maintenance, including skincare. The searches further included clinical and other research studies relevant to rosacea, treatment, maintenance, and skincare use as an adjunct in the English language from January 2010 to December 2020. Excluded were articles with no original data (unless a review was deemed relevant), articles not dealing with skincare for treatment and maintenance, and publication language other than English.

In addition, a dermatologist and a physician/scientist (the reviewers) conducted the searches on August 16 and 17, 2021 on PubMed and Google Scholar as a secondary source of the English-language literature, using the terms:

Rosacea, pathophysiology, skin barrier dysfunction in rosacea, lipid abnormalities in rosacea-prone skin, prescription treatment and maintenance, rosacea guidelines, algorithm, consensus recommendations. OTC rosacea skincare and sunscreen use, cleansers and moisturizers for rosacea treatment, maintenance, adjunctive treatment, efficacy, safety, tolerability, skin irritation of OTC skincare use, quality of life aspects, handling and comfort, treatment adherence.

The results of the searches were evaluated independently by the two reviewers, resolving discrepancies by discussion. The searches yielded one hundred and sixty-eight publications. After reviewing the abstracts, the publications lacking data contributing to the current algorithm [n = 104] were removed, leaving 64 papers. Thirty-four papers remained after excluding duplicates and articles deemed irrelevant for the algorithm ([n = 30] other subjects, low quality, a small number, case studies). Twenty-five review articles (including sixteen guidelines, algorithms, and systemic literature reviews) and nine clinical studies were used in the development of the algorithm.

FIGURE 2. Algorithm for treatment and maintenance of cutaneous rosacea features.



Sun protection factor (SPF), Erythema (ETR), Ultraviolet (UV), Once a day (q.d.), Pulsed Dye laser (PDL), Neodymium-doped yttrium aluminum garnet (Nd: YAG), Twice daily (b.i.d.), Benzoyl peroxide (BPO), Oral contraceptive pill (OCP).

Rating the level of evidence of topical and systemic prescription treatments for rosacea was outside the scope of this publication.[23] In addition, the small number of clinical studies on skin barrier dysfunction and skincare using cleansers and moisturizers for rosacea as an adjunct to treatment and maintenance did not allow for grading.[23]

Algorithm for Cutaneous Rosacea Treatment and Maintenance Integrating Skincare

The USCRO algorithm for cutaneous rosacea treatment and maintenance used the mnemonic RECUR (Reliable, Efficient, Clear instructions, Understandable, Remember easily).[24] A clinical algorithm's function is to standardize and support medical decision-making, such as regulating the selection and use of treatment regimens, thereby improving adherence to evidence-based guidelines.[21-24] The algorithms have inputs and outputs, precisely defined specific steps, and uniquely defined results that depend on the preceding steps.[24] The current algorithm for managing and maintaining rosacea focuses on promoting a healthy skin barrier reducing and managing the signs and symptoms of rosacea, and integrating OTC products and skincare (Figure 2). Detailed information on aspects of rosacea diagnosis, the main concern or rosacea subtype, is given in Box 1.

Foundational measures to be taken by all patients with rosacea and rosacea-prone skin are detailed in the algorithm. These measures include education, behavioral modifications, avoidance of triggers and skin irritants, preventative skincare, and sun avoidance and sunscreen use. Finally, the algorithm describes how assessment of skin condition and grading of cutaneous rosacea should take place during treatment and maintenance while the preventative measures continue. Each section is discussed in order as they appear in the algorithm.

Box 1: Diagnosis of rosacea focusing on the various phenotypes that are present.

Diagnostic features:
- Fixed centro-facial erythema
- Phymatous changes

Major:
- Flushing
- Papules and pustules
- Telangiectasia
- Ocular manifestations

Secondary:
- Symptoms of itch/sting
- Ocular symptoms

The presence of persistent centro-facial erythema associated with periodic intensification and phymatous changes is sufficient for the diagnosis of rosacea. Two or more major features such as inflammatory papules/pustules, flushing, and telangiectasia are diagnostic of the disease. Symptoms of itch, burn, and ocular symptoms only contribute to the diagnosis of rosacea if they appear in combination with other features.

Foundational Measures for All Rosacea Patients

Is rosacea a skin barrier disorder?

The discussion of "what comes first, the chicken or the egg" is relevant to many aspects of the pathogenesis of rosacea, including inflammation, skin microbiome dysbiosis, and loss of antimicrobial peptides.[6,16-20] Studies in rosacea patients showing skin barrier deficiency such as increased TEWL, decreased hydration, and elevated skin surface pH point towards rosacea being a barrier defect disorder but are not conclusive.[6,10-20]

One study investigated the difference in skin barrier function and the cutaneous microbiome between lesional and non-lesional areas of papulopustular rosacea.[16] The pilot study, including 25 patients, showed that rosacea's physiological features (lower water content and higher TEWL) are closely associated with changes in the skin microbiome.[16] The main skin surface microorganisms include *Propionibacterium, Staphylococcus,* and low-abundant bacteria.[18] There is a significant decrease in *cutibacterium acnes (c. acnes)* in rosacea-prone skin, which may be of pathological significance.[25,26]

Staphylococcus epidermidis tends to form biofilms when concentrations of *c.acnes* decrease.[25,26] *Demodex* mites play a role in rosacea; however, it remains unknown whether rosacea-affected skin favors *Demodex*, causing dysbiosis, or whether the mites themselves contribute to disease progression.[27,28]

There are important associations between skin barrier deficiency and microbiome dysbiosis in many skin diseases, including rosacea.[19,20] However, it has not been clearly delineated whether the dysbiosis triggers rosacea or dysbiosis is a response to skin changes resulting from rosacea-induced inflammation.[6,16]

Some rosacea patients have overlapping conditions, such as seborrheic dermatitis, acne, or perioral dermatitis, complicating treatment and maintenance. Rosacea is a great imitator of other conditions, and it is, on occasion, challenging to diagnose.[6]

Diagnosis of cutaneous rosacea

In the last ten years, expert and consensus groups have called for the replacement of subtype classification with phenotype descriptors.[1,3] Rosacea may be considered in the presence of at least one diagnostic sign.[1,3,29-33] These signs include persistent redness of the central facial skin and thickened skin in the central face (phymatous changes).[1,3,29-33] Major signs include papules, pustules, flushing, telangiectasias, and eye irritation.[1,3,29-33] Secondary signs and symptoms, such as burning or stinging, edema, and dryness, may also develop but are not diagnostic.[1,3,29-31]

Rosacea's various phenotypes may appear in other combinations and at different times.[29] Research suggests that all are manifestations of the same underlying disease process and that rosacea may progress in severity and include additional phenotypes (Box 1).[3,29-33] According to the authors,[3,29-33] a patient's phenotypic characteristics and symptomatology are more consistent with the patient's individual experience than the older subtype classification, which may not fully cover the range of clinical presentations and is likely to confound severity assessment.

Education and behavioral measures

Rosacea patients need education on the chronic and recurrent nature and the triggers of the condition.[6] The USCRO advisors agree that early education of patients on rosacea prevention, treatment, and maintenance measures, including skincare, is an important step in building a therapeutic relationship with the patients enabling their active participation in the treatment plan.[6,34-36] Before starting the rosacea treatment, a detailed discussion between the patient and the treating clinician should address the treatment and maintenance protocol, potential side effects, diagnostic tests, management of adverse events (AEs), and preventative measures (Box 2).[6] The discussion should be supported by written or digital material to allow the patient to process the information.[34-36] This session's outcome should be: 1) The patient has been educated on the nature of her/his disease along with the role of lifestyle interventions. 2) The patient expresses an understanding of prevention measures such as avoiding triggers, using skincare and sun protection measures.[6,34-36] 3) The patient understands the medications and OTC products for treatment, and maintenance, proper skincare, and how to access the relevant information.[6,34-36]

Box 2: Education and behavioral measures for all rosacea patients.

Education:

- Provide detailed patient education on the skin changes that have and may occur.
- Have a detailed discussion with the patient, explaining preventative measures, the treatment protoco, and maintenance.
- Explain the condition and rationale for applying cleansers, moisturizers, and sunscreen to prevent, treat the condition, and maintain improvement. Demonstrate the application process. Solicit input and questions. Provide instruction sheets or digital information and websites for later home reference and education.

Behavioral measures:

- Avoid triggers and irritants, for example: Sun exposure, hot or spicy food, hot beverages, alcohol, physical exercise, high-temperature environments, abrupt changes of temperature, vasodilators, or angiogenic drugs.

Note: Irritants can include skincare irritants, such as harsh cleansers (surfactants, exfoliants), astringents, alkaline skin and haircare products, and fragrance.

Box 3: Skincare with cleansers and moisturizers.

- ***Skincare formulations*** should be safe, effective, free of additives, fragrances, perfumes, or sensitizing agents. Cleansers and moisturizers should have a near-physiological skin pH (4.0–6.0).50
- ***Gentle cleansers:*** Use non-greasy, syndets or lipid-free cleansers with a near physiologic pH (4-7) in a gentle cleansing motion with the fingertips. Avoid hot or cold water, cleansing brushes, and scrubs. Avoid the use of soap and cleansers with an alkaline pH (>7), which may excessively remove skin lipids, elevating skin surface pH, and compromise the skin barrier function further.
- ***Moisturizers:*** Use fragrance- and sensitizing agent-free moisturizers preferably containing physiologic lipids such as ceramides. Choose a moisturizer vehicle based on skin condition, level of xerosis, and patient preference. Moisturizer effectiveness depends on the formulation, vehicle, frequency, and compliance of applications. Skincare product choices depend on the skin condition, availability, costs, and individual preferences.

The National Rosacea Society (NRS) raises public awareness and supports research, and provides medical professionals with patient education and professional tools.[34] A further source of information is physicians' patient education on rosacea.[35]

Skincare and UV protection

Addressing barrier repair early in the treatment phase, continuing such care through acute treatment, and maintenance are paramount in rosacea management.[6,9,10] Regardless of its origin, the disturbed barrier often results in the inability of the patient to use the medications and products that would otherwise result in clinical improvement.[6,9,10] A previously published review by the USCRO advisors on skin barrier deficiency in rosacea and the integration of OTC products and skincare explored recent guidelines and algorithms for rosacea management to provide a basis for OTC recommendations.[2,6,30,32,37-39-42] The advisors confirmed that guidelines recommend skincare with gentle cleansers and moisturizers to relieve and prevent dry skin, improve irritation symptoms, and restore skin barrier function.[2,6,30,32,37-42] According to the guidelines, skincare should include a gentle cleanser, avoidance of topically applied triggers, use of a moisturizer containing barrier lipids such as ceramides, and a sunscreen.[2,6,30,32,37-42]

Cleansers

A gentle cleanser has a near-physiological skin surface pH (4-6) and does not disrupt the beneficial lipids, proteins, and normal flora that contribute to the skin barrier's integrity and function.[6,15,43-45] The advisors felt that using a foaming cleanser may not be suitable for rosacea patients.[6] Ingredients to be avoided are fragrances, perfumes, soaps, surfactants, detergents, and products with an alkaline pH (>7). These have been found to elevate skin surface pH, which in turn depletes

skin lipids, and reduces microbial diversity, which is explicitly damaging for rosacea patients.[6]

Moisturizers

Quality moisturizers contain humectants to attract water and occlusives that form a barrier that retains water by preventing TEWL.[6,12,15,32,43-45] Moisturizers containing lipids such as ceramides, cholesterol, and free fatty acids further help to restore the skin barrier function and maintain its integrity.[6,15,32,43-45]

Alpha hydrox acid (AHA) containing products can change the skin microbiome and surface pH and result in irritation.[6,15,32,43-45] Good skincare helps to improve stratum corneum hydration, reduce TEWL, and maintain skin softness and elasticity.[6] Challenges to implementing a skincare regimen include complex regimens and applications viewed as a "chore," personal preferences, socioeconomic factors, and cost (Box 3).[6,51]

Sun protection measures and products

UV radiation exposure is an important trigger for rosacea in mary patients.[1,2,4]

Guidelines recommend, and the panel agreed, that sun avoidance and sunscreen with a sun protection factor (SPF) of at least 30 are necessary for rosacea patients.[2,6,30,32,37-42] Sunscreens are part of a complete program for sun protection that includes protective clothing and sun avoidance. [2,6,30,32,37-42] Sunscreens can be classified as UVB filters, UVA1, UVA2 filters, or physical blockers.[46-49] Most currently available sunscreen formulations aim to cover both UVA and UVB spectra. Physical blockers, including zinc oxide, are effective in UVA and UVB ranges as they reflect or refract UV radiation.[46-48] A ceramide-containing sunscreen and moisturizer routine protects against UV-induced skin surface barrier changes by preventing erythema and hyperpigmentation, improving skin hydration, and maintaining normal superficial skin cells morphology and turnover.[49]

Many dermatologists recommend daily sunscreen of SPF 30 or higher, especially for sun-exposed areas, 15 minutes before sun exposure and every 2 hours after that (Box 4).

Box 4: UV protection.

- Avoid unprotected sun exposure, and use a sunscreen with a sun protection factor (SPF) of at least 30.
- Physical sunblocks contain zinc oxide or titanium dioxide may be less irritating.
- Re-apply sunscreen every 2 hours when outdoors, or more often if sweating or swimming. Use a broad-brimmed hat if going outside and avoid being in direct sunlight between 10 AM and 4 PM.

Treatment and Maintenance of the Main Phenotype

This section of the algorithm defines three areas of main concern, 1) erythema, 2) telangiectasia, and 3) papules and or pustules. Patients with rosacea usually present with a spectrum of findings.[6,31] To effectively target the disease, there is a need to treat all of the individual anomalies in each patient.[6,30-33] Erythema and telangiectasia are often cited by patients as being the most bothersome signs.[6,30-33] Other findings, such as central facial edema, stinging, and burning, are equally bothersome.[6,30-33]

Evaluation of prescription medications was outside the scope of this work. Prescription treatments and maintenance appear in the algorithm as recommended in current guidelines and consensus papers and described in the USCRO review by the advisors (Table 1).[2,6,30-32,37-42]

Guidelines recommend that persistent erythema be treated with topical brimonidine or topical oxymetazoline.[2,6,31-32,37-43] Patients with both erythema and telangiectasia may benefit from laser and intense pulsed light therapy; however, laser may not be suitable for richly pigmented skin types.[5] FDA-approved therapy for the papules and pustules of rosacea includes oral doxycycline 40 mg modified-release (MR), topical azelaic acid, topical metronidazole, topical ivermectin, topical minocycline foam, and, most recently, microencapsulated benzoyl peroxide.[6] Although isotretinoin is not FDA approved for this indication, it is effective for recalcitrant disease and phymas. [2,6,30-32,37-43] Further treatment options for the papules and pustules of rosacea include antibiotic doses of doxycycline, minocycline, and sarecycline, although antibiotic resistance concerns preclude long-term use.[2,6,30-32,37-43,54] Prescription medications combined with formulated gentle cleansers, moisturizers, and sunscreen support successful rosacea therapy; however, specific beneficial ingredients for rosacea are not well defined and require more studies.[6,45,50,51]

CONCLUSION

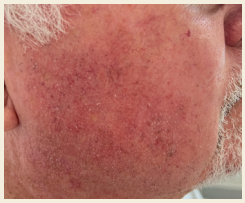
The USCRO evidence-based clinical treatment and maintenance algorithm combines prescription medications with gentle cleansers and moisturizers for rosacea phenotypes. Addressing facial skin barrier repair early in the treatment phase, continuing such care through acute treatment, and maintenance is paramount in rosacea management.

DISCLOSURES

The authors disclosed receipt of an unrestricted educational grant from CeraVe USA for support with this work's research. The authors also received consultancy fees for their work on this project. All authors contributed to the development and review of this work and agreed with the content.

TABLE 1.

Evidence of Topical and Systemic Medications for Rosacea Included in the Algorithm

Concern or Phenotype	Treatment	Evidence
Erythema 	Topical brimonidine or topical oxymetazoline	≥1 RCT – no major design flaws
	Intense pulsed light therapy	≥1 RCT– no major design flaws
	Laser (PDL and Nd:YAG)	Prospective clinical trials ≥20 participants. No adequate controls or lacking another key facet of the design
Telangiectasia 	Oral B-blockers	Small trials (<20 participants), significant design limitations
	Botulinum toxin	Case series >5 participants
	BPO, sodium-sulfur/sulfur	Case series >5 participants
	Intense pulsed light therapy	≥1 RCT– no major design flaws
	Laser (Pulsed Dye laser (PDL) and Nd:YAG	Prospective clinical trials ≥20 participants. No adequate controls or lack of another key facet of the design Not suitable for richly pigmented skin
Papulopustular rosacea 	*FDA-approved therapy:* Oral doxycycline 40 mg modified release. Topical azelaic acid, topical ivermectin, topical minocycline, topical microencapsulated BPO, and topical metronidazole	≥1 RCT– no major design flaws
	Hormonal medications (OCP, spironolactone)	Small trials (<20 participants), significant design limitations
	Not FDA approved for this indication: Isotretinoin is effective for most aspects of recalcitrant disease and phymas	Prospective clinical trials ≥20 participants. No adequate controls or lacking another key facet of the design
Maintenance	Topical ivermectin, metronidazole, minocycline, topical retinoids, azelaic acid. Consider combination treatment with systemic treatment.	≥1 RCT– no major design flaws Doxycycline and minocycline, although antibiotic resistance concerns preclude long-term use
	Topical microencapsulated benzoyl peroxide.	≥ RCT– no major design flaws

Randomized controlled trial (RCT), Pulsed Dye laser (PDL), Neodymium-doped yttrium aluminum garnet (Nd: YAG), Benzoyl peroxide (BPO), Oral contraceptive pill (OCP)

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