Standard Management Options for Rosacea: the 2019 Update by the National Rosacea Society Expert Committee

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Abstract

In 2017 a National Rosacea Society expert committee developed and published an updated classification of rosacea to reflect current insights into rosacea pathogenesis, pathophysiology, and management. These developments suggest that a multivariate disease process underlies the various clinical manifestations of the disorder. The new system is consequently based on phenotypes that link to this process, providing clear parameters for research and diagnosis, as well as encouraging clinicians to assess and treat the disorder as it may occur in each individual. Meanwhile, a range of therapies has become available for rosacea, and their roles have been increasingly defined in clinical practice as the disorder has become more widely recognized. This update is intended to provide a comprehensive summary of management options, including expert evaluations, to serve as a guide for tailoring treatment and care on an individual basis to achieve optimal patient outcomes.

Capsule summary

- Since 2009, there has been a dramatic increase in scientific knowledge about rosacea's pathophysiology and comorbidities, as well as additional FDA-approved therapies.
- The updated management options provide an opportunity for more comprehensive and better-informed patient care, based on the phenotypes that reflect the needs of each individual case.

Overview

Rosacea is a chronic inflammatory disorder of the facial skin that primarily affects the cheeks, nose, chin, forehead, and eyes, often characterized by remissions and exacerbations. Cutaneous features include persistent facial erythema, phymas, papules, pustules, telangiectasia, and flushing.[1] Rosacea has been most frequently observed in fair-skinned individuals, but has been increasingly diagnosed in Asians, Latin Americans, African-Americans, and Africans.[1,2] In epidemiological studies of Caucasians, the incidence of rosacea has been 10 percent or higher, and a recent analysis of worldwide epidemiological data estimated that rosacea may affect 5.5 percent of the population on a global basis.[3] The disorder is diagnosed more often in women than men, and onset typically occurs after age 30, though it may develop at any age. The density of *Demodex* mites is often found at higher levels in rosacea patients than in those without the disorder.[4]

Rosacea's unsightly and conspicuous appearance often has significant emotional ramifications, potentially resulting in depression or anxiety, and frequently interferes with social and occupational interactions.[5-14]

Ocular manifestations occur in more than 50 percent of those with rosacea, and may appear before or in the absence of cutaneous features.[15] Symptoms may include dryness, burning and stinging, light sensitivity, blurred vision, and foreign body sensation. External, readily apparent signs include lid margin and conjunctival telangiectases, plugging of the meibomian glands, and chalazia. In advanced disease patients may present with chalazion affecting the eyelid. Severe ocular rosacea may lead to corneal inflammation and scarring and, conceivably, corneal perforation, with loss of visual acuity.[16]

Although causal relationships have not been determined, recent studies have found an association between rosacea and increased risk of a growing number of systemic disorders, including cardiovascular, gastrointestinal, neurological, and autoimmune diseases, as well as certain types of cancer. These findings further elevate the clinical significance of rosacea as growing evidence of its potential link with systemic inflammation is increasingly understood,[17-32] though in many disorders there may be either conflicting study results or there is only one study to suggestion the association.

History

In 2009, the National Rosacea Society (NRS) assembled a consensus committee and review panel of 26 experts to develop standard management options for the disorder as described in the standard classification and grading systems for rosacea, published in 2002 and 2004, respectively.[33,34] The original classification system designated common patterns of signs and symptoms as subtypes, and was intended to be updated as scientific knowledge and clinical experience increased.

In practice, the subtype designations were widely interpreted as distinct entities, which tended to limit consideration of the full range of potential signs and symptoms as well as the frequent simultaneous occurrence of more than one subtype or the potential progression from one subtype to another. In addition, subsequent research uncovered important new insights into rosacea's pathogenesis and pathophysiology, and suggest that a consistent multivariate disease process underlies the various clinical manifestations of the disorder.

To fulfill the directive of the original authors, a committee and review panel of 28 experts was convened by the NRS to develop an updated standard classification system, published in the *Journal of the American Academy of Dermatology* in 2018.[1] Based on phenotypes to reflect current knowledge of its pathophysiology, the new standard classification

of rosacea provides a means of assessing rosacea so that therapy can be personalized in a manner consistent with each patient's individual experience.

As a further step, the committee has now developed recommended management options for rosacea based on these standard criteria to assist in providing optimal patient care. Because it is fundamental to consider the broad spectrum of potential therapies in the treatment of rosacea, the consensus committee and review panel have been broadened to include 27 clinical experts in dermatology, laser therapy, skin care, and ophthalmology.

The committee reviewed the relevant literature and met to discuss the extent of evidence as well as the level of efficacy of various therapies. The discussion was captured via audio recording, and a first draft was prepared with input from all participants. The draft was then reviewed and edited by all committee members, and was finalized only after all assessments were unanimously approved. The document was then further reviewed by the panel of additional rosacea experts, and virtually all edits and comments were accepted by the committee.

As with the updated standard classification system, the proposed standard management options are considered provisional and may be updated as scientific knowledge increases and additional therapies become available.

Diagnosis and assessment

There is no definitive laboratory test for rosacea, and diagnosis is based on clinical observation as well as a patient history, which can be essential as some features may not be visually evident or present at the time of the patient visit. Features identified in the new standard classification system are listed in Table I, including diagnostic, major, and secondary (minor).[1]

When assessing treatment, the committee noted that patients' perception and acceptance of their facial appearance – including its impact on their emotional, social, and professional

lives – may be important in determining the level of therapy. Patient surveys have suggested that the psychosocial burden of rosacea may be substantial regardless of severity,[4-6] and the goal of achieving an investigator global assessment (IGA) of 0 for inflammatory papules and pustules may often be appropriate and feasible.[35] It may also be advisable to remind patients that normalization of skin tone and color is the goal rather than complete eradication of facial coloration, which can leave the face with a sallow appearance.

Management options

Although there is no cure for rosacea, its features may be reduced or controlled with a range of topical and oral therapies and light devices, as well as appropriate skin care and lifestyle management. Combination therapy to target the specific features of each rosacea patient is often necessary for effective treatment. The treatments listed in Tables II-IV are intended to serve as a menu of options rather than a treatment protocol.

While data is limited on the efficacy of many medical therapies, recent systematic evaluations have also found variability in the quality of evidence.[36,37] Patients and features of the disease may respond well or less well to various agents, and when treatments are effective, the mechanism(s) of action may be unclear. Consequently, the Tables represent the committee's expert opinion, comprising knowledge and experience as well as data, on the therapies' relative efficacy. Increasing efficacy is indicated with a range from one to four circles, with 'N' for not applicable, and the circle density is used to indicate the strength of supporting trial evidence, with solid as strong and open as weak.

Although rosacea's features may appear in different combinations and at different times, research has found that all appear to be manifestations of the same underlying inflammatory continuum.[1] Therefore, any particular therapy may prove to be acting on an aspect of that continuum. Recent studies point to a multivariate set of pathogenic pathways, including defects

in the innate and adaptive immune systems, mast cells and related biochemical mechanisms, and the neurovascular system.[38-54] The phenotype approach may also result in the discovery of biomarkers and the development of more precise measuring systems.

Drugs

The FDA-approved topical therapies for inflammatory papules/pustules of rosacea include azelaic acid, 15%; ivermectin cream, 1%; metronidazole 1% and 0.75%; and sodium sulfacetamide 10% in various formulations. Modified release oral doxycycline capsules, 40 mg (30 mg immediate release and 10 mg delayed release beads), were approved by the FDA for the treatment of inflammatory papules/pustules of rosacea with a lower dosage than that of doxycycline used to treat infections, and have been associated with fewer side effects and shown to be safe for long-term use. The use of this agent has not been associated with the development of bacterial resistance.[55] Topical and oral therapy are often initially prescribed in combination, followed by long-term use of a single therapy alone to maintain remission.[56-59]

When first-line treatments for inflammation are inadequate or when rosacea is more severe, off-label oral antibiotics or retinoids are sometimes used, though there is little data. These may include tetracycline, doxycycline, minocycline, and oral isotretinoin. Prevention of pregnancy during treatment with the latter is crucial, and management includes routine pregnancy tests and adherence to pregnancy prevention protocols. Tetracycline should also be avoided in pregnancy as fetal and maternal toxicity have been reported and use during tooth development may cause tooth discoloration.

The FDA-approved topical therapies for the treatment of persistent facial erythema of rosacea in adults include brimonidine topical gel, 0.33%, an alpha-adrenergic agonist, and oxymetazoline hydrochloride cream, 1%, an $alpha_{1A}$ adrenoceptor agonist.

Off-label use of various drugs has sometimes been prescribed to help control flushing, including nonsteroidal anti-inflammatory drugs, antihistamines, clonidine, and beta-blockers.

Light devices

Though the quality of clinical evidence is limited, two types of laser, pulsed-dye and potassium titanyl phosphate (KTP), are well established in practice and have been shown to be highly effective in removing telangiectasia and diminishing erythema.[60,61] Intense pulsed light (IPL) has been found effective in reducing flushing, in improving the health of the ocular surface, and on decreasing the interference of meibomian gland disease on activities of daily living.[62-64]

Ablative lasers such as CO_2 (carbon dioxide) and erbium, as well as radiofrequency and surgical shaving, can be appropriate for removing tissue from and resculpting the rhinophymatous nose. Although laser therapies can be helpful as noted, all laser therapies should be used with caution only by highly trained professionals in patients with darker skin.

Ocular rosacea therapy

Ocular rosacea may appear as a spectrum of disease, from dry eye to blepharitis to meibomian gland dysfunction, all of which may be related to underlying inflammation. Approximately 20 percent of patients have ocular findings before dermatological evidence of rosacea, and the diagnosis may not be clear in those who never progress to the cutaneous form of the disorder.[15]

The mainstays of treatment for ocular rosacea are eyelash hygiene and oral omega 3 supplementation, followed by topical azithromycin or calcineurin inhibitors. The patient should apply a warm compress and cleanse the eyelashes twice daily with baby shampoo on a wet washcloth rubbed onto the eyelashes of the closed eyes.[65] Antibiotic ointment may be used to

decrease the presence of bacteria and to soften any collarettes, allowing easy removal by the patient during eyelash hygiene. Topical cyclosporine drops may be additive in decreasing the topical inflammation in these patients. An oral tetracycline such as modified release, subantimicrobial doxycycline may also be used.[66] In recent studies topical azithromycin has been demonstrated to be equally as effective as oral doxycycline, with fewer side effects in the treatment of the ocular manifestations of rosacea.[67-71] For severe ocular rosacea other oral medications may be prescribed by an ophthalmologist. Any corneal ulceration, inflammation, or red eye should be immediately referred to an ophthalmologist, as it may result in reduced visual acuity.

In experienced hands, IPL for cutaneous rosacea phenotypes has been found to elicit improvement in ocular rosacea signs and symptoms as well, suggesting a field effect.[72-76] In addition, effective devices are available that improve inspissated meibum using thermopulsation that decreases symptoms of irritation.[77-79]

Lifestyle management

Because rosacea is characterized by flare-ups and remissions, its standard management options include lifestyle changes and adjunctive care in addition to drug therapies and light devices. Some of rosacea's exacerbations may often appear to be initiated by environmental and lifestyle factors – often related to flushing as well as the development of papules and pustules. Avoidance of those factors affecting the individual patient may help maintain remission.

Clinicians may advise patients to keep a daily diary of lifestyle and environmental factors that appear to affect their rosacea in order to help identify and avoid their personal triggers. Surveys have found the most common factors to be sun exposure, emotional stress, hot weather, wind, heavy exercise, alcohol consumption, hot baths, cold weather, spicy foods,

humidity, indoor heat, certain skin-care products, heated beverages, certain medications, medical conditions, certain fruits, marinated meats, certain vegetables, and dairy products.[80]

As the disorder's unsightly appearance and unpredictability of flares often negatively affect the social and occupational aspects of patients' lives, this in turn may become a source of stress that can trigger further exacerbation in an adverse and self-propagating spiral.[6-14]

Skin care

Gentle skin care is an important component of rosacea management, as patients with rosacea often have skin that is sensitive and easily irritated, causing redness, burning, and stinging. Thus the goal of daily skin care for rosacea patients is to maintain the integrity of the skin barrier while avoiding agents that aggravate inflammation or flushing.

As sun exposure may be a leading influence on the development of flushing and erythema, patients are advised to always use sunscreens, preferably mineral inorganic products that contain zinc oxide or titanium dioxide, because they do not produce heat as a byproduct and provide physical rather than potentially irritating chemical protection. Mineral-based sunscreens primarily reflect and secondarily absorb UV radiation as zinc oxide and titanium dioxide are coated with silicone to prevent the generation of secondary oxygen radicals resulting from UV absorption, although one recent study suggests absorption may be the primary mechanism of protection.[81] There are also options, which include micronized, nanoparticle, and clear formulations, for rosacea sufferers with darker skin, as past formulations left a chalky white or grayish appearance.

There is a plethora of mass-market over-the-counter topical skin care products that claim to soothe the skin and reduce the appearance of redness. Though there is sparse data to validate the claims, such products will typically contain one of the following nonprescription

ingredients: sunscreen, sulfur, and botanical substances including allantoin, bisabolol (a chamomile-derived extract), licorice root extracts (with licochalcones as the active agent), willowbark (active agent, a salicylate), or aloe vera (active agent a salicylate and alloemodin). While forms of sulfur and botanical ingredients may potentially account for a degree of anti-inflammatory effect, published clinical studies for the treatment of specific disease are generally not available.

As with other skin care products, patients may be advised to select cleansers and nonocclusive moisturizers that do not irritate their skin.[81] Patients should be directed to a gentle cleansing regimen, using a syndet (synthetic detergent) or nonirritating cleanser, washing the face gently, and waiting for the face to completely dry before applying topical therapy or other products, as stinging is more likely to occur when the skin is wet. Cosmetics, especially those with a green or yellow tint, may be effective in reducing the appearance of redness. However, as with cleansers and moisturizers, care should be taken to minimize irritation, and patients should be advised to avoid any products that cause burning, stinging, itching, or other discomfort.

Conclusion

The explosion of rosacea research over the past 15 years has led to a dramatic increase in our understanding of this disorder affecting all skin types that is now beginning to produce significant improvements in the physical health and quality of life for rosacea patients as advances in therapy continue. It now appears that rosacea is caused by a multivariate process and is a disorder whose wide range of features are manifestations of the same underlying inflammation, offering the potential for more precise assessment and treatment of individual patients as well as newly identified inflammatory pathways for the development of new therapies. The new phenotype-based standard classification and management of rosacea provide

important insights and guidance for the selection of treatments and broad spectrum of care to achieve optimal patient outcomes.

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Table I. Features of rosacea.
*These features by themselves are diagnostic of rosacea.
†Two or more major features, typically in a centrofacial distribution, may be considered diagnostic.

Table II. Treatment options for diagnostic features.
Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak. C, used in combination therapy only.
**Skill dependent; postinflammatory hyperpigmentation risk.

Table III. Options for major features.
Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak. C, used in combination therapy only.

Table IV. Options for ocular rosacea.
*On lashes, pulsed 1-2 weeks/month for 3-6 months.
**2-3 months; long-term use causes topical steroid rosacea-like reaction.
Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak.

Table I. Features of rosacea[1]		
Diagnostic*	**Major†**	**Secondary**
Fixed centrofacial erythema in a characteristic pattern that may periodically intensify	Flushing	Burning sensation
Phymatous changes	Papules and pustules	Stinging sensation
	Telangiectasia	Edema
	Ocular manifestations • Lid margin telangiectasia • Interpalpebral conjunctival injection • Spade-shaped infiltrates in the cornea • Scleritis and sclerokeratitis	Dryness
		Ocular manifestations • "Honey crust" and collarette accumulation at the base of the lashes • Irregularity of the lid margin • Evaporative tear dysfunction (rapid tear breakup time)

*These features by themselves are diagnostic of rosacea.

†Two or more major features, typically in a centrofacial distribution, may be considered diagnostic.

Table II. Treatment options for diagnostic features			
	Persistent erythema	Phymas	
		Active (Inflamed)	Fixed (Not inflamed)
Topical therapies			
Brimonidine[56,83]	◦ ◦		
Oxymetazoline[84]	◦ ◦		
Retinoids[56,85-89]		◯/C	
Devices and surgical interventions			
IPL[56]	◯◯		
PDL[56]	◯◯		
KTP	◯◯		
CO_2[56, 85-89]		C	◯◯◯◯
Erbium[56, 85-89**]		C	◯◯◯◯
Cold steel[56, 85-89**]		C	◯◯◯◯
Electrosurgery[56, 85-89**]		C	◯◯◯◯
Radiofrequency[56, 85-89**]		C	◯◯◯◯
Oral therapies			
Carvedilol	◯		
Doxycycline (subantimicrobial)	◯	◯/C	
Doxycycline	◯	◯/C	
Minocycline	◯	◯/C	
Tetracycline	◯	◯/C	
Isotretinoin		◯◯/C	
Azithromycin		◯/C	
Trimethoprim/sulfamethoxazole		◯/C	

Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak. C, used in combination therapy only.
**Skill dependent; postinflammatory hyperpigmentation risk.

Table III. Options for major features			
	Papules/pustules	Telangiectasia	Flushing

Topical therapies			
Ivermectin[56,90-94]	▪ ▪ ▪		◯
Azelaic acid[56,95]	▪ ▪		
Metronidazole[56,87,96-103]	▪ ▪		
Clindamycin[56]	◯		
Retinoids	◯	◯	
Sulfacetamide sodium/sulfa	◯		
Brimonidine[36,59]	C		◯
Oxymetazoline			◯
Oral therapies			
Doxycycline (subantimicrobial)[56,104]	▪ ▪ ▪		
Azithromycin[36]	◯◯◯		
Doxycycline[56,105]	◯◯◯		
Minocycline[36]	◯◯◯		
Isotretinoin[56,106,107]	◯◯◯		
Trimethoprim/sulfamethoxazole	◯◯◯		
Tetracycline[56,108,109]	◯◯		
Clindamycin	◯		
Carvedilol[84,85,109]			◯
Clonidine[85,86,110]			◯
Propranolol[85,86,110]			◯
Light devices			
IPL[1]		◯◯◯◯	◯◯
PDL[1]		◯◯◯◯	
KTP		◯◯◯◯	◯

Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak. C, used in combination therapy only.

Table IV. Options for ocular rosacea

	Ocular
Topical therapies	
Azithromycin[67-71]*	◯◯◯
Cyclosporin[56]**	◯◯◯

Tacrolimus*	◯◯◯
Oral therapies	
Cyclosporin[56]**	◯◯◯
Azithromycin[99]	◯◯
Doxycycline (subantimicrobial)[111]	◯◯
Doxycycline[111,112]	◯◯
Minocycline[66]	◯◯
Tetracycline	◯
Sulfamethoxazole-trimethoprim	◯
Light devices	
IPL[65]	◯

*On lashes, pulsed 1-2 weeks/month for 3-6 months.

**2-3 months; long-term use causes topical steroid rosacea-like reaction.

Number of circles indicates the committee's expert opinion on relative efficacy up to four, with four indicating the most effective. Filled versus open circles indicate strength of trial evidence, with solid circles as strong and open circles as weak.