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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Wise (editor) reports he is on the speakers bureau for the Medicines Company. Dr. Endly (author), Dr. Zaidi (author), Dr. Perkins (author), Dr. Miller (author), Dr. Solomon (peer reviewer), Ms. Coplin (executive editor), and Ms. Mark (executive editor) report no financial relationships relevant to this field of study.

AHC Media

Rosacea: An Overview of the Pathophysiology, Clinical Features, and Treatment

A common chronic skin condition that affects adults, rosacea is characterized by a wide spectrum of signs and symptoms. Patients classically experience facial flushing and erythema, telangiectasias, facial swelling, papules, and pustules involving the convexities of centrofacial areas such as the cheeks, nose, chin, and forehead. A key diagnostic finding is diffuse background erythema of these areas that worsens during a flare.^{1,2} A flare is often referred to as flushing and results from sudden vasodilation of superficial blood vessels in the skin.^{2,3} Because of the variety of potential rosacea presentations, the National Rosacea Society assembled a committee of rosacea experts to establish a subtype classification system to aid in diagnosis and appropriate treatment.⁴ The National Rosacea Society's consensus committee described four subtypes and one variant, all of which can range in severity from mild to moderate to severe. (See Table 1.)

Rosacea is most often seen in Caucasians or individuals with lighter skin types and is rarely seen in African Americans. Reports of rosacea prevalence vary from 1.34% to 22%, but these results are confounded by numerous differences and shortcomings in study designs.⁵⁻⁹ The typical age of onset is between 30 and 50 years of age, but the condition can present earlier or later in life as well. The underlying cause of rosacea is poorly defined with many remaining unknowns. Several of the suspected contributing factors include genetic factors, an aberrant innate immune response, vascular hypersensitivity, ultraviolet radiation, microorganisms, and skin barrier dysfunction.

Pathophysiology

Genetic Factors

A patient's particular genes may contribute to his or her development of rosacea as an adult. Of those with rosacea, 10-20% report a family history of rosacea.¹⁰ The higher incidence of rosacea in those of Celtic or Northern European descent also suggests a possible genetic component. Still, several genomic studies have failed to pinpoint a causative gene.¹¹

Innate Immune Response

The innate immune system serves as the body's nonspecific, acute

EXECUTIVE SUMMARY

Rosacea is a common, chronic skin disorder characterized by facial flushing, erythema, and telangiectasias that worsen during flares.

- Rosacea is most commonly seen in Caucasians, with prevalence reports ranging up to 22%.
- The underlying cause is poorly defined but contributing factors include aberrant immune response, vascular hypersensitivity, UV radiation, microorganisms, and skin barrier dysfunction.
- The classification system identifies four subtypes and one variant.
- Erythematotelangiectatic subtype has persistent erythema with overlying telangiectasias and episodic flushing. These

patients are best managed with sun protection, gentle skin care, and lasers that target the hypervascular component.

- Papulopustular subtype displays persistent erythema with transient papules and pustules on the central face. Treatment typically involves the use of topical or systemic antibiotics.
- Phymatous subtype is a more rare occurrence in which the patient experiences patulous follicles with debilitating enlargement, most commonly of the nose. When severe, successful treatment requires surgical modalities.
- Ocular subtype may present with eyelid swelling, erythema, and scale, as well as conjunctivitis and a burning or stinging sensation of the eye. Management is similar to papulopustular rosacea.

defense mechanism against infections and other environmental stimuli. When triggered, it leads to the controlled release of numerous cytokines and antimicrobial peptides in the skin. The innate immune system seems to be disrupted in patients who have rosacea.

In 2007, Yamasaki et al illustrated that facial skin from patients with rosacea displays unusually elevated levels of an antimicrobial peptide called cathelicidin as well as cathelicidin's processing enzyme, a serine protease called kallikrein 5.¹² Kallikrein 5 cleaves cathelicidin into a smaller, active peptide called LL-37. In addition to being more

abundant, the LL-37 found in those with rosacea is smaller than in those unaffected by rosacea. These mutant forms of LL-37 are able to upregulate the innate immune system with resultant inflammation and angiogenesis.¹³ Yamasaki et al further demonstrated this concept with a study that involved the injection of cathelicidin peptides from rosacea patients into murine skin that led to inflammation and vasodilation.^{14,15}

Vascular Hypersensitivity

Persistent background centrofacial erythema and telangiectasias remain a key diagnostic clue to the diagnosis of rosacea. An acute,

transient worsening of facial erythema, known as flushing, can occur after exposure to various triggers.¹⁶ (See Table 2.) Flushing occurs when a trigger results in an exaggerated vasodilation response by cutaneous vasculature. For example, compared to controls, patients with rosacea were found to flush more readily after heat exposure.¹⁷ Other possible triggers include spicy foods or alcohol, but the exact mechanism of how these dietary factors play a role in the pathogenesis has yet to be elucidated. Various medications, such as amiodarone, topical steroids, nasal steroids, and high doses of vitamins B6 or B12, are other less

Table 1. Subtypes and Variants of Rosacea and Their Major Characteristics⁴

Subtype	Characteristics
Erythematotelangiectatic	Persistent central facial erythema with flushing ± telangiectasia
Papulopustular	Transient papules and pustules overlying persistent central facial erythema
Phymatous	Prominent pores with thickened, nodular areas of enlargement, most commonly affects the nose
Ocular	Conjunctivitis, periorbital edema, blepharitis, chalazia, and hordeola on exam with complaints of foreign body sensation, burning, or stinging
Variant	
Granulomatous	Hard brown, yellow, or red monomorphic papules or nodules

Table 2. Potential Triggers for Facial Flushing and Worsening of Rosacea^{16,19}

Rosacea Triggers	Patients Affected
Sun exposure	81%
Stress	79%
Heat	75%
Wind	57%
Strenuous activity	56%
Alcohol consumption	52%
Cold weather	46%
Spicy foods	45%
Certain skin care products	41%
Hot beverages	36%
Medications	15%
Source: Author adapted.	

frequently described potential rosacea triggers.^{18,19} One study found the endothelial cells lining blood vessels and lymphatics in those with rosacea express higher levels of vascular endothelial growth factor (VEGF), CD31 (an endothelial cell marker), and D2-40 (a lymphatic endothelial marker).²⁰ This knowledge further supports the idea of vascular hypersensitivity and excessive endothelial stimulation of cutaneous vasculature in those with rosacea.

Ultraviolet Radiation

Ultraviolet (UV) exposure and photodamage have been proven to play an important role in the pathophysiology of rosacea. Most patients with rosacea, regardless of subtype, report worsening of their rosacea along with flushing after being out in the sun. Additionally, the clinical findings of rosacea are most prominent on areas that suffer the highest levels of UV exposure (i.e., protuberant or convex areas of

the face). UVA radiation increases the expression of matrix metalloproteinases (MMPs) and denatured collagen in the skin.²¹ MMPs are zinc-containing proteases that break down various components of the extracellular matrix, resulting in damage to blood vessels and the dermal matrix. Exposure to UVB radiation leads to the production of VEGF and other angiogenic factors from keratinocytes, further contributing to the hypervascularity seen in those with rosacea.²² In general, UV radiation generates reactive oxygen species (ROS), which have a pro-inflammatory effect on the skin. ROS bind to toll-like receptor 2 (TLR2) on keratinocytes, which only further propagates the inflammatory cascade occurring in rosacea.¹⁵ The epidermis in those with rosacea expresses higher amounts of both ROS and TLR2 than in those without rosacea.^{23,24}

Microorganisms

Demodex mites are a normal

commensal organism found within the pilosebaceous units of facial skin. However, many studies have found a higher density of mites on the skin of patients with rosacea when compared to unaffected individuals.²⁵ It is unclear whether these mites are a possible trigger for rosacea or rather a response to the numerous changes in the skin's microenvironment. Regardless, several studies suggest they play some role in the multifactorial pathophysiology that drives rosacea.

When mites are numerous and infest a pilosebaceous unit, an intense peri-follicular infiltrate of mainly CD4+ helper T-cells can be seen on histology.²⁶ *Demodex* mites also contain the bacterial organism *Bacillus oleronius*, which also may play a pro-inflammatory role. One study closely examined antigenic proteins from the *B. oleronius* bacterium and revealed these proteins have the potential to stimulate an inflammatory response in patients with rosacea.²⁷ The mites also release chitin, which can activate TLR2 on keratinocytes.²⁸ Thus, *Demodex* mites and *B. oleronius* both appear to contribute to the dysregulation of the local innate immune response seen in rosacea.

Skin Barrier Dysfunction

A majority of patients with rosacea complain of "sensitive skin" and report dry facial skin with a stinging or burning sensation. As discussed earlier, serine protease levels are elevated in those with rosacea, and this may result in epidermal barrier dysfunction. A stinging or burning sensation results when a sensory irritant, such as lactic acid for example, easily penetrates the skin through a disruption or abnormality in the epidermal barrier.²⁹ Individuals with rosacea also have been found to have increased transepidermal water loss resulting in dry, sensitive skin.³

Clinical Features

The primary clinical features

of rosacea most often involve the convexities of the central face and include non-transient background erythema, flushing (transient erythema), papules, pustules, and telangiectasias. Additionally, numerous secondary signs and symptoms may accompany the primary clinical features above. Some of the secondary features of rosacea include dry skin with a burning or stinging sensation, elevated red inflammatory plaques, facial edema, ocular manifestations, and phymatous changes.

Rosacea has a wide variety of clinical presentations and can exhibit different combinations of the above-described clinical features. Thus, the National Rosacea Society formed a committee to design a standard classification system for rosacea and described four subtypes of rosacea and one variant.⁴ The classification system resulted in a standard terminology to allow precise diagnosis and treatment of all subtypes of rosacea. The four subtypes and one variant are described in further detail below and summarized in Table 1. All subtypes typically begin mild and can progress to moderate or severe if untreated.

Erythematotelangiectatic Rosacea

Patients with this subtype mainly are characterized by a background of persistent facial erythema, frequent episodes of flushing, and telangiectasias. (See Figure 1.) Some of the more common secondary findings include central facial edema and dry skin with a stinging or burning sensation. These patients are typically fair-skinned and, thus, many clinicians find it challenging to differentiate erythematotelangiectatic rosacea in these individuals from chronic actinic damage, also known as dermatoheliosis. Dermatoheliosis even may exhibit flushing with temperature changes. However, patients with dermatoheliosis usually present later in life, have evidence or history of precancer or non-melanoma skin cancers,

Figure 1. Erythematotelangiectatic Subtype of Rosacea



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and do not display facial edema or complain of a stinging or burning sensation.

Papulopustular Rosacea

The key clinical feature of papulopustular rosacea is a temporary eruption of several small, dome-shaped, erythematous papules overlying persistent centrofacial erythema. (See Figure 2.) The papules may appear in crops or can be solitary and a pustule may surmount some. Typically, the papules resolve after about two weeks with no

resultant scarring. These features should not be confused with those of seborrheic dermatitis or acne vulgaris. Seborrheic dermatitis typically presents with erythematous patches and a greasy, yellow scale involving the centrofacial creases (i.e., nasolabial folds) and eyebrows. This is in comparison to rosacea's involvement of the convexities (protuberant areas), not the folds, of the central face. Papulopustular rosacea is commonly mistaken for acne vulgaris in younger patients, but can be differentiated by its lack

Figure 2. Papulopustular Subtype of Rosacea



Image used with permission from Dr. Jere Mammino

of comedones, also known as whiteheads and blackheads.

Phymatous Rosacea

Phymatous rosacea arises from hypertrophy of the sebaceous glands and thickening of the skin that results in nodules and enlargement of the affected area. The earliest clinical indication of phymatous rosacea is dilated pores, or patulous follicles. As the disease progresses, the hypertrophy of the tissue creates distortion of the affected areas with soft, nodular growths. Rhinophyma, or thickening of the nose, is the most common type of phymatous rosacea and predominantly occurs in males.³⁰ (See

Figure 3.) Rarely, phymatous rosacea may occur in other locations such as the central chin, central forehead, lower ears or earlobes, and eyelids as outlined in Table 3.^{4,10} Phymatous rosacea rarely may occur in other locations, such as the central chin (gnathophyma), central forehead (mentophyma), lower ears or earlobes (otophyma), and eyelids (blepharophyma).^{4,10} Phymatous rosacea is commonly misperceived as end-stage rosacea; however, many patients have mild or no preceding rosacea.¹⁰

Ocular Rosacea

The clinical features of ocular rosacea are varied and nonspecific.

Some of the nonspecific ocular complaints that patients may report include itching, tearing, dry eyes, a gritty sensation, blurred vision, and frequent styes. On exam, the patient's eyes typically appear watery and may display conjunctival injection, tiny concretions in the eyelashes referred to as conical dandruff, and eyelid erythema. (See Figure 4.) Some patients suffer from a recurrent chalazion, a non-infectious cyst involving the meibomian glands, or hordeolum, a chronic staphylococcal infection of the zeis or meibomian glands. Up to 20% of patients with ocular rosacea have no accompanying cutaneous findings of rosacea and, thus, arriving at a diagnosis with certainty is very challenging in these cases.³¹ More commonly, ocular rosacea is seen in patients who also have one of the other subtypes of rosacea.

Granulomatous Rosacea

Granulomatous rosacea is considered a clinical variant of rosacea rather than a specific subtype. The key clinical feature is hard, skin-colored, yellow, brown, or red papules or nodules that typically arise on the cheeks or periorificial skin. These bumps do not seem to be inflammatory in comparison to the papules and pustules seen in papulopustular rosacea. They are also monomorphic in each affected patient and overlay normal-appearing skin. Granulomatous rosacea typically does not coexist with any of the subtypes of rosacea. A biopsy of the affected area reveals granulomas with central necrosis and, thus, requires the clinician to perform further studies to rule out sarcoidosis and tuberculosis.³²

Treatment Options

Due to the multifactorial pathophysiology and numerous subtypes of rosacea, management spans a wide spectrum of treatment modalities. In general, a thorough history should be taken to evaluate for all possible exacerbating factors. The

Figure 3. Rhinophyma Seen in Phymatous Subtype of Rosacea



Image used with permission from Dr. Jere Mammino

patient then should be counseled on the importance of avoidance or moderation of the identified triggers.

General Skin Care Recommendations

Rosacea patients are encouraged to cleanse their faces twice daily with lukewarm water and a soap-free, pH-balanced cleanser. The cleanser should not have any scrubbing particles or harsh antibacterial agents. Then, they should apply a fragrance-free moisturizer to help combat the excessive dryness and increased transepidermal water loss.²⁹ There are numerous over-the-counter topical cosmeceutical creams that are rich in antioxidants and may decrease the amount of reactive oxygen species in the skin contributing to rosacea.³³ Although in general, heat can still induce a

Table 3. Various Types of Phymatous Rosacea¹⁰

Phyma	Clinical Characteristics
Rhinophyma	Early on: dilated, patulous follicles most prominent at distal nose Later on: enlarged, nodular, deformed nose that often leads to debilitation and psychological implications for the patient
Gnathophyma	Rare occurrence that results in enlargement of the central chin
Otophyma	Hypertrophy of the dermis and adnexal structures of the lower half of the helices and earlobes
Mentophyma	Presents as a firm, swollen plaque that is cushion-like on the central forehead
Blepharophyma	Thickening and edema of the eyelids; this finding is not limited to phymatous rosacea, as it may be seen in severe papulopustular or ocular rosacea as well
Source: Author adapted.	

Figure 4. Mild Ocular Rosacea



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flare, regular photoprotection is key to reduce the possibility that UV exposure will trigger a rosacea flare.³⁴ Although no specific sun-screen agent has been proven to be superior for those with rosacea, the general recommendation is to apply sun-blocking agents that contain titanium dioxide or zinc oxide with a sun protection factor of 30 or higher.

Categorizing patients by their subtype of rosacea is especially useful when specific treatment options are being considered. Patients then can be classified further according to their disease severity. This also can help the clinician to determine the most appropriate treatment regimen. The best treatment options for each subtype of rosacea are discussed below and summarized in Table 4.

Erythematotelangiectatic Rosacea

Patients with mild erythematotelangiectatic rosacea have mild fixed facial erythema and intermittent flushing, but no telangiectasias. Treatment for these patients typically focuses on the general skin

care recommendations discussed previously. As disease severity progresses to moderate and severe, patients begin to have more frequent flushing and several telangiectasias. If the patient expresses concern about the centrofacial erythema, a topical alpha-adrenergic receptor agonist (such as brimonidine) may be applied to the entire face in the morning. This typically results in direct vasoconstriction within one hour of application and a visible reduction in facial erythema.³⁵ Telangiectasias require the use of lasers such as pulsed dye and potassium-titanyl-phosphate lasers.³⁶ Metronidazole, a common topical antibacterial agent used to treat rosacea, has been found to be ineffective in the treatment of erythematotelangiectatic rosacea and often causes irritation in patients with this subtype.³⁷

Papulopustular Rosacea

Topical and systemic antibiotics are the mainstay of treatment for papulopustular rosacea. Systemic antibiotics, such as doxycycline, typically are used to treat

papulopustular flares. They are prescribed in short courses, typically four to six weeks, as opposed to longer regimens of up to six months when used for acne. Patients who suffer from moderate or severe papulopustular rosacea may require frequent courses of oral antibiotics.

After successful treatment of a flare, patients are encouraged to continue treatment with topical antibiotics for maintenance therapy. In a large Cochrane review, metronidazole gel or cream and azelaic acid gel were the only topical treatments shown to effectively minimize papulopustular rosacea relapses.³⁷ A more recent trend in the treatment of rosacea uses sub-antimicrobial doses of doxycycline. Sub-antimicrobial doses have anti-inflammatory effects and may be efficacious for all severities of papulopustular rosacea.³⁸ This dosing regimen of doxycycline offers the advantages of once daily dosing and avoidance of antibiotic resistance, and doxycycline is the only FDA-approved oral treatment for papulopustular rosacea.³⁶

Phymatous Rosacea

Mild phymatous rosacea typically presents with dilated pores and a small amount of hypertrophy. In 2010, Gollnick et al conducted a study that demonstrated oral isotretinoin as an efficacious and well-tolerated treatment option for mild phymatous rosacea.³⁹ Moderate-to-severe phymatous rosacea demonstrates even further hypertrophy with distortion of the normal contour and, thus, requires surgery.¹⁰ Various surgical methods include complete surgical excision or incomplete excision via dermabrasion, electrosurgery, or CO₂ laser ablation. These surgical modalities remove the hypertrophied sebaceous glands and connective tissue with minimal complications and satisfactory cosmetic results.⁴⁰

Ocular Rosacea

People who suffer from mild ocular rosacea have minimal

Table 4. Treatment Options for Rosacea According to Subtype¹⁰

Erythematotelangiectatic Rosacea	
Treatment	Comments
General skin care recommendations	Especially helpful, as this subtype is prone to “sensitivity”
Photoprotection	UV radiation potentiates dermal matrix damage
Topical brimonidine (alpha-agonist)	Results in vasoconstriction to temporarily improve erythema
Laser therapy	Pulsed dye and KTP improve telangiectasias
Papulopustular Rosacea	
Treatment	Comments
Metronidazole cream or gel	Can be used to clear inflammatory lesions or as an indefinite maintenance therapy
Azeleic acid gel	More effective than metronidazole ± more irritation
Sodium sulfacetamide and sulfur lotion	
Erythromycin solution	Solution is alcohol-based and poorly tolerated
Clindamycin lotion	
Benzoyl peroxide and clindamycin	May cause skin irritation
Tretinoin cream or gel	May improve associated photodamage; some poorly tolerate it
Permethrin cream	As effective as metronidazole for papules
Systemic Treatments	Comments
Antimicrobial doxycycline	100 mg once to twice daily for 4-12 weeks
Sub-antimicrobial doxycycline	40 mg daily (30 mg immediate release, 10 mg delayed release)
Minocycline	100 mg twice daily for 4-12 weeks
Azithromycin	250-500 mg three times a week for flares or maintenance
Isotretinoin	10-40 mg daily
Source: Author adapted.	

clinical findings, but complain of a dry, gritty sensation in the eyes. Cleansing the eyelid margins with a mild shampoo and using artificial tear replacement appears to be adequate for mild ocular disease.¹⁰ As severity increases, patients

begin to develop conjunctivitis, crusting of the eyelids, and complain of burning, stinging, blurred vision, and chalazion or hordeolum. Moderate-to-severe ocular rosacea often requires topical and systemic antibiotics as outlined above for

papulopustular rosacea.

Conclusion

Rosacea is a chronic inflammatory skin condition that primarily affects the protuberant areas of the central face. Patients

Table 4. Treatment Options for Rosacea According to Subtype (Continued)¹⁰

Phymatous Rosacea	
Treatment	Comments
Isotretinoin	May reduce nasal volume and halt progression
Surgical excision	Can effectively debulk and resculpt the nose
Other surgical modalities	Electrosurgery, dermabrasion, and CO ₂ laser
Ocular Rosacea	
Treatment	Comments
Eyelid hygiene and artificial tears	Frequently effective for mild disease
Fusidic acid drops	Useful after oral antibiotics to maintain remission
Metronidazole gel	Same as above
Systemic antibiotics per above	Treats moderate to severe disease

Source: Author adapted.

often experience exacerbations and remissions of various clinical features such as facial flushing, erythema, telangiectasias, edema, papules, pustules, ocular lesions, and phymatous changes. Each patient with rosacea has a unique presentation, but most patients fit into one or more of the four subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular). The exact pathophysiology of rosacea remains unknown. However, various factors, such as genetics, innate immune system, vascular hypersensitivity, ultraviolet radiation, microorganisms, and skin barrier dysfunctions, all are proposed to play some role. All patients with rosacea should follow a gentle skin care regimen. The most common prescription treatments involve topical or systemic antibiotics. Ultimately, it is important to be able to distinguish rosacea from other cutaneous diseases, such as acne vulgaris, chronic actinic damage, or seborrheic

dermatitis, to ensure successful treatment. One should not hesitate to refer a challenging or recalcitrant case to dermatology to rule out other possible less common dermatologic conditions.

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CME Questions

1. A 40-year-old female with a history of central facial redness and flushing following alcohol consumption presents to the office with a chief complaint of papules on her nose and cheeks. What is the best treatment choice?
 - a. Daily sunscreen
 - b. Oral doxycycline
 - c. Erythromycin solution
 - d. Tretinoin cream
2. What is the most frequently reported trigger in rosacea?
 - a. Sun exposure
 - b. Alcohol
 - c. Spicy foods
 - d. Exercise
3. Which topical treatment for papulopustular rosacea has been shown to be more effective than metronidazole?
 - a. Clindamycin
 - b. Permethrin
 - c. Tretinoin
 - d. Azeleic acid
4. The pathogenesis of rosacea is largely unknown. Which of the following have been found to be elevated in the skin of rosacea patients?
 - a. Kallikrein
 - b. Cathelicidin
 - c. VEGF
 - d. All of the above
5. A 45-year-old female requests an immediate treatment for her erythematotelangiectatic rosacea for a wedding she will be attending in five days. Which is the best option for rapid yet transient improvement of erythema without significant cosmetic effects?
 - a. Tretinoin cream
 - b. Clindamycin topical
 - c. Topical bromonidine
 - d. Metronidazole cream
6. A 38-year-old male presents to discuss his increasingly enlarging face. He feels as though his nose has become bumpy and deformed over the past year. His forehead feels thicker and cushion-like. Which of the following refers to the phymatous changes described on his forehead?
 - a. Rhinophyma
 - b. Mentophyma
 - c. Gnathophyma
 - d. Otophyma

PRIMARY CARE REPORTS

CME Objectives

- Upon completion of this educational activity, participants should be able to:
- Summarize recent, significant studies related to the practice of primary care medicine;
 - Evaluate the credibility of published data and recommendations related to primary care medicine;
 - Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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