

# Rosacea: A Review CME

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## Introduction

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Rosacea is a common disease among the fair-skinned, but it may be seen in all skin types. Disease severity varies greatly and is to some degree in the eye of the beholder at the mild end of the spectrum. Indeed, mild rosacea in New York might well be considered normal in Dublin.

## Epidemiology

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Rosacea is thought of as a disease of the fair, but this is not exclusively the case. Persons of any ethnic group may be afflicted. Features of rosacea may be seen in childhood or extreme old age, but typically the disease is at its worst in the 30s through the 50s.<sup>[1,2]</sup> Exact incidence data are lacking because it is difficult to define when the disease begins and how to differentiate early vascular rosacea from sun damage. A Swedish study reported an incidence of 10%, which seems realistic.<sup>[3]</sup> Data on the incidence in various racial and ethnic groups are generally lacking, but it is reasonable to say that disease incidence -- and detection -- is higher in lighter-skinned people.

## Etiology

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Despite its long history, the causes of rosacea are only beginning to be understood, largely because science has only recently had the tools to explain the disease.

There are clear neurologic influences in rosacea. Patients give a history of easy blushing and flushing and over time report a general reddening of the complexion, which may be promoted by chronic sun exposure. Wilkin<sup>[4]</sup> has shown that the vasodilation of rosacea patients is greater and more persistent than that seen in normal volunteers. Wilkin has also clearly shown that in most cases thermal stimuli are the cause of food-induced flushing<sup>[5,6]</sup>; it is the temperature of the coffee rather than the caffeine that causes a blush. Although rosacea is not commonly thought of as a neurologic disease, it must be remembered that blushing is a neurally mediated function and that rosacea thus partly has a neurologic basis. Indeed, studies report an increased incidence of rosacea in parkinsonism.<sup>[7]</sup>

Why vasodilation promotes rosacea is not clear. It has been proposed that minute amounts of plasma are extravasated by the blush and induce an inflammatory response that increases with repeated episodes of vasodilation, resulting in smoldering inflammation analogous to the dermatitis seen in chronic leg edema.<sup>[5]</sup> It is also possible that blushing is genetically linked to rosacea but is not causal, much as ichthyosis and atopy are linked but are pathogenetically unrelated.

Patients with rosacea also have a defective skin barrier and may be hyperirritable. Patients often complain of stinging and burning from cosmetics and medications. Dirschka and colleagues<sup>[8]</sup> and Laquieze and colleagues<sup>[9]</sup> demonstrated increased transepidermal water loss in the skin of patients with rosacea or perioral dermatitis.

Cathelicidin and serine protease activity are also clearly involved in the pathogenesis of rosacea and may be central to the disease. Gallo and colleagues<sup>[10]</sup> have demonstrated that elevated epidermal serine protease activity occurs in rosacea and causes the deposition of cathelicidin-derived peptides in the skin. These peptides have the ability to cause inflammation when injected in the skin.

A link between barrier function and inflammation may be provided by the findings of Voegeli and colleagues,<sup>[11]</sup> who showed that defective barriers have elevations in serine proteases that normalize when the barrier is corrected.

An apparent association between *Helicobacter pylori* and rosacea has been reported,<sup>[12-14]</sup> but subsequent studies have clearly demonstrated that the association is merely the coincidence of 2 common conditions that happen to respond to the same medications.<sup>[15-19]</sup>

*Demodex folliculorum* is a mite that lives within the lumen of the sebaceous follicles of the head and has been implicated in rosacea, but the evidence is largely circumstantial. Lacey and colleagues<sup>[20]</sup> have demonstrated in vitro that Demodex has antigens that react with sera from rosacea patients and is capable of stimulating the proliferation of mononuclear cells.<sup>[20-25]</sup> Follicles with Demodex in residence may be shown to have a surrounding inflammatory response.<sup>[26,27]</sup> Problems establishing a Demodex etiology in rosacea include the difficulty of sampling follicular contents in a rigorous manner and the fact that most rosacea medications do not affect the mite but do improve the disease. Conversely, treatment with lindane does not improve rosacea in this author's experience. Until new data appear, it seems that Demodex, at most, may be an exacerbating factor in predisposed individuals.

## Clinical Features

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The clinical presentation of rosacea is varied. Its 4 primary subtypes are erythematotelangiectatic (ie, vascular), inflammatory (ie, papulopustular), phymatous, and ocular. There are also several variants, including granulomatous, pyoderma faciale, perioral dermatitis, and steroid rosacea.<sup>[28]</sup>

### Erythematotelangiectatic (Vascular) Rosacea

The earliest possible clinical stage of vascular rosacea is a recurrent blush. Whether this constitutes rosacea is arguable. With time, the blush may become more long-lasting and eventually become fixed; telangiectasias begin to form (Figure 1). In some individuals, larger spider angiomas develop. It appears that the size of telangiectasias is determined to some degree by the amount of sun damage that has occurred.



**Figure 1.** Vascular rosacea. (Image courtesy of dermnet.com)

Whether a healthy blush warrants a diagnosis of rosacea is rightfully a matter of controversy. In the view of many experts, rosacea does not begin until erythema is constant, at a minimum.

Edema is sometimes a clinical feature of rosacea. Recurrent vasodilation results in a feeling of cheek fullness that is sensed by patients, and the physician can often discern subtle induration of the cheeks. This edema typically responds slowly to tetracyclines. A variant of rosacea in which a persistent woody induration develops that is responsive to isotretinoin has also been noted.<sup>[29,30]</sup>

### **Inflammatory Rosacea**

The spectrum of inflammation in rosacea is similar to that of acne and runs from small papules and pustules to deep, persistent nodules. Reflecting the vasoreactivity of the individual, rosacea papules are a deeper red than similar papules in acne. Also in distinction to acne, rosacea lesions are not centered around a comedo or perhaps even a follicle, and defects in follicular keratinization play no role in the process. Typically, inflammation is greatest on the central cheeks (Figure 2) but can also occur on the rest of the face (Figure 3) and rarely the center of the chest. The most common lesions are small papulopustules, but large granulomatous nodules may also occur.



**Figure 2.** Inflammatory rosacea. (Image courtesy of dermnet.com)



**Figure 3.** Inflammatory rosacea affecting the forehead. (Image courtesy of dermnet.com)

### **Sebaceous Hyperplasia**

Overgrowth of sebaceous glands may be a prominent feature in some rosacea patients. Rhinophyma, a nasal sebaceous hyperplasia, is clearly linked to the disease. Initially, the skin of the nose becomes slightly swollen and smoother. Pores become more apparent as keratinous debris accumulates and glandular tissue swells. Gradually, a lumpy surface develops (Figure 4). Histologically the process is

initially one of sebaceous overgrowth and then fibrosis. Patients should be made aware that rhinophyma is uncommon in rosacea and that progression to rhinophyma is not the norm. Women in particular are unlikely to develop the condition.



**Figure 4.** Rhinophyma. (Image courtesy of dermnet.com)

### **Ocular Rosacea**

Although underappreciated, ocular rosacea is extremely common, with some ophthalmologic series reporting an incidence of 50% in rosacea patients. Although this figure may be a bit elevated due to patient recruitment bias, it is clear that ocular rosacea is common. Symptoms range from a sensation of dryness or tired eyes to edema, tearing, pain, blurry vision, styes, chalazia, and corneal damage. Physical findings include blepharitis (Figure 5), meibomian impaction, styes, keratitis, corneal neovascularization, and corneal ulceration and even rupture.



**Figure 5.** Rosacea blepharitis. (Image courtesy of dermnet.com)

Ocular rosacea has been attributed to tear-film acidity, but more recent studies disprove this concept. It is now thought that meibomian gland impaction leads to decreased lipid in the tear film, greater tear evaporation, and subsequent irritability of the eye.<sup>[31-33]</sup> Epithelium-derived protease activity, particularly matrix metalloproteinase 9 (MMP9), is elevated in ocular rosacea tear fluid. In vitro studies have shown that MMP9 is inhibited by doxycycline.<sup>[34,35]</sup>

### **Perioral Dermatitis**

Perioral dermatitis and periocular dermatitis often appear in patients with vascular rosacea but minimal malar inflammation (Figure 6). Clinically, small pink papules and pustules recur over weeks to months. Various environmental sensitivities have been reported in individual patients, but a generally applicable explanation is lacking.<sup>[36]</sup> The link to rosacea is not certain but is probable; the histopathology is similar to rosacea,<sup>[37]</sup> and the diseases occur in the same population and respond to the same medications.



**Figure 6.** Perioral dermatitis. (Image courtesy of dermnet.com)

### **Pyoderma Faciale**

Eruptions of inflamed papules and yellow pustules in the centrafacial region has been termed pyoderma faciale or rosacea fulminans. Like periorificial dermatitis, pyoderma faciale is linked to rosacea in that it is similar histologically and responds to some of the same medications.<sup>[38,39]</sup> Patients are typically younger and are more often female, and the disease may begin with very little prior history of rosacea. In many cases, the patient has been treated for various infections without success.

### **Steroid Rosacea**

Long-term use of corticosteroids -- whether topical or systemic -- inevitably results in the exacerbation of rosacea. Initially the rosacea improves, but after prolonged use, atrophy, persistent vasodilation, and inflammatory papules develop.<sup>[40,41]</sup> The presence of rosacea-like lesions on the upper lip and around the ala nasi is a clue to steroid involvement. Fluorinated and other potent steroids cause problems more quickly, but any topical or inhaled steroid<sup>[42]</sup> is probably capable of inducing rosacea. Often there is no clear history of steroid use. Steroids have been reported to have been surreptitiously added to many homeopathic products, especially bleaching creams. Withdrawal of the steroid is required and might as well be done abruptly. This author has found that gentle tapering of steroid use is rarely effective. The flare of rosacea will be dramatic upon steroid withdrawal and can be blunted by oral therapy with prednisone, doxycycline, minocycline, or isotretinoin. Topical tacrolimus has also proven to be very helpful in these patients,<sup>[43,44]</sup> although pimecrolimus, a similar molecule, has yet to be found effective in rosacea.<sup>[45]</sup>

### **Histopathology**

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Histologic changes in mild forms of rosacea are subtle and often are limited to vascular ectasia and mild edema. As the process advances, a perivascular and perifollicular lymphohistiocytic infiltrate and elastolysis develop. The most severely inflammatory forms of the disease show noncaseating epithelioid granulomas and sinus tract formation.<sup>[46]</sup>

## Differential Diagnosis

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### Seborrheic Dermatitis

Seborrheic dermatitis often coexists with rosacea. Ocular rosacea is frequently misdiagnosed as seborrheic dermatitis and thus is improperly treated.

### Keratosis Pilaris

Facial keratosis pilaris can be difficult to differentiate from rosacea, and at times the 2 diseases may coexist. A fixed blush, especially on the lateral cheeks, with fine follicular keratotic plugs characterizes facial keratosis pilaris.

### Growth Factor Receptor Inhibitor "Acne"

This acute eruption that may occur during chemotherapy can resemble severe acne or rosacea in some patients. Timing with chemotherapy is diagnostic.

### Lupus Erythematosus

The malar erythema associated with lupus erythematosus can be hard to differentiate from rosacea, and indeed many lupus patients have coexistent rosacea that flares when systemic steroids are tapered. The presence of pustules and papules or blepharitis favors a diagnosis of rosacea. Fine scaling, pigmentary changes, follicular plugging and scarring, and tenderness favor lupus.

### Acne Vulgaris

Typically, acne vulgaris occurs in a younger age group than does rosacea and is characterized by comedonal lesions. Patients in their 20s and 30s may have both diseases simultaneously. In this presentation, the acne most commonly occurs on the jawline of women.

## Therapy

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Rosacea can be a difficult disease to treat, at least in part because the predisposing vasodilation is largely unresponsive to topical or systemic therapy (with the exception of corticosteroids, which are contraindicated). Avoidance of obvious vasodilators and irritants is clearly helpful in some patients.

### Topical Therapy

Topical metronidazole is the major topical therapy for rosacea.<sup>[47-49]</sup> Applied once or twice daily, it is most active on inflammatory lesions and may have some effect on erythema, especially perilesional erythema. Response is not immediate; sometimes several weeks are required before a benefit is seen.

Azelaic acid cream is useful in rosacea and in one study appeared to be about as effective as topical metronidazole.<sup>[49]</sup> Nonirritating benzoyl peroxide preparations are also useful in treating the inflammatory forms of rosacea.<sup>[50]</sup> Topical erythromycin, clindamycin, and tetracycline appear to have little effect on rosacea.

Topical tretinoin has been reported to be helpful over the long term in rosacea,<sup>[51]</sup> perhaps counterintuitively because it is an irritant in many patients. The drug's effect is clearly not on follicular keratinization but may be on the elastolysis seen in chronic rosacea.

## Oral Therapy

Tetracyclines are the most commonly prescribed oral drug for rosacea.<sup>[52-54]</sup> Their mechanism of action is primarily anti-inflammatory in rosacea because there is no bacterial stimulus for the disease. The anti-inflammatory activity of this family of drugs is well described.<sup>[55,56]</sup> Tetracyclines decrease the chemotactic response of neutrophils, inhibit metalloproteinases, inhibit granuloma formation, and inhibit protein kinase C.<sup>[57]</sup>

Tetracyclines can be given in surprisingly low dosages, such as 20 mg twice daily.<sup>[58]</sup> More recently, a 40-mg sustained-release doxycycline has become available that is effective as initial therapy and has the advantage of being below the level of antimicrobial activity.<sup>[59]</sup> There is justifiable concern about antibiotic overuse, the spread of resistant organisms, and the possibility that long-term rosacea treatment might exacerbate resistance. This drug is designed to be purely anti-inflammatory; antimicrobial levels of the drug are never achieved and there is no change in the microbial flora of the skin or gastrointestinal tract. Therefore, resistance cannot develop.

Other antibiotics are occasionally useful in rosacea. Trimethoprim/sulfamethoxazole and ciprofloxacin<sup>[54]</sup> both improve inflammatory rosacea but are rarely used because of cost and valid concerns about the generation of resistant bacteria populations. Erythromycin, penicillins, and cephalosporins are of very little use in rosacea.

The most severe forms of rosacea may require isotretinoin therapy.<sup>[51,60]</sup> Inflammatory lesions and particularly refractory nodules typically respond well to 0.25 to 1 mg/kg isotretinoin. Unfortunately, a lasting response, as is seen in the treatment of acne, does not occur frequently, and patients may require long-term maintenance therapy with oral tetracyclines. The mechanism by which isotretinoin is effective in rosacea is unclear because its main mode of action in acne -- inhibition of the sebaceous gland -- would appear not to be operative in inflammatory rosacea. Isotretinoin is also helpful in rhinophyma. The best results are achieved when treatment is begun before significant fibrosis has developed.

## Surgical Treatments

Telangiectasias and persistent erythema are effectively treated with intense pulsed light or the pulsed-dye laser.<sup>[61,62]</sup> Lasting remissions of vascular rosacea are sometimes achieved. Electrocoagulation of telangiectasias is also effective but carries a greater risk for scarring. CO<sub>2</sub> laser or hot-loop recontouring is the only treatment that can improve fibrotic rhinophyma.

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