

## Common Diseases: Treatment Options

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# Rosacea

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**A** 65-year-old man of Celtic descent presented for treatment of facial erythema and papules (Figures 1, 2). He had never sought treatment before, but his daughter wanted him to have a dermatologist examine his condition. He turned intensely erythematous while drinking alcoholic beverages. He declined oral antibiotics because he did not want to take pills, and pulse dye laser because of the cost. He decided to be treated with topical metronidazole 0.75% gel twice daily for 6 weeks. At his follow-up visit, his face was about 20% less erythematous and he said he was flushing and blushing less and wished to continue with the topical regimen.

### Discussion

Rosacea, most basically conceptualized, is sensitivity of facial skin. Rosacea clinically manifests as erythematous flushing, blushing, telangiectasia, papules, and pustules. In areas of long-standing rosacea, blood-orange colored plaques can develop (phymas), most commonly on the nose (rhinophyma). Manifestations are divided into four variants, which often occur simultaneously: erythematotelangiectatic, papulopustular, phymatous, and ocular. Certain pathogens appear to be associated with rosacea. (Table I).<sup>1,2</sup>

Rosacea is usually progressive (it worsens) in the long term, but cyclic (it waxes and wanes), in the short term. Rosacea has a variety of triggers (Table II)<sup>1,2</sup> that induce or exacerbate it. When patients who suffer from rosacea present for treatment, they complain of flushing and blushing, and sensitive skin. In particular, they complain that their skin is irritated by topical preparations. Rosacea has a substantial psychosocial impact on the lives of patients.

Epidemiologically, rosacea is most common in persons of northern and western European descent with a fair complexion. As such, rosacea is a common condition in the United States and Western Europe. In a Swedish survey of people between the ages of approximately 20 and 60, about 10% were estimated to have rosacea, with a 3:1 incidence in women compared with men.<sup>3</sup> In the United States, 10–20 million people are thought to suffer from rosacea, although a greater number will experience simple nonprogressive flushing from a variety of triggers—in particular, the drinking of alcohol.<sup>1,2</sup> Rosacea is uncommon in children. It is first noticed as flushing in patients in their twenties, most commonly becomes troublesome to patients in their thirties, and progresses thereafter. In the United States, consistent with the Swedish study mentioned above, rosacea is more common in women than in men.

A variety of treatments (Table III)<sup>4–14</sup> are available for rosacea, but unlike acne, which can be cured by isotretinoin, no rosacea treatment tends to be curative. No precise treatment algorithm has become the standard of care; treatment is empiric. Treatment with topical metronidazole is probably a good place to start. Sulfur products can be used to treat rosacea, but whether they are more effective than metronidazole is unclear. In the treatment of rosacea, sulfur products can provide patients a soothing, nonirritating means of cleansing the skin. The gold standard of oral treatment is tetracycline-type antibiotics, of which minocycline seems to be most effective. If azithromycin, which is now available in generic form, is comparatively priced to minocycline and doxycycline, its minimal side effects, lack of drug interactions, and three-time-a-week dosing should make it an initial agent. Newer

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**Figure 1.** Cheek of patient with rosacea demonstrating telangiectasia and a few erythematous papules



It is unclear whether rosacea has seasonal variation or is associated with UV radiation. Some have suggested that it is worse in the spring, but this might be the result of confusion of rosacea with the panoply of photosensitivity disorders.<sup>1,2</sup> Harsh wind and sunlight can worsen rosacea, according to some authorities, but this is not a proven association. As rosacea occurs most commonly in Fitzpatrick type 1 skin, it would seem that topical and oral rosacea treatment should be accompanied by sunscreens or sunblocks—in particular, metallic agents such as zinc oxide or titanium dioxide.

Variants of rosacea exist beyond the four basic types of rosacea. Rosacea fulminans, which manifests as multiple erythematous papules, pustules, nodules, and purulent discharging cysts, is a severe incarnation of rosacea. It can be treated by prednisone 0.5–1 mg/kg, followed by oral isotretinoin. Particularly in people of color, rosacea can also occur as firm flesh-colored papules, termed granulomatous rosacea. The entity described as Lupus miliaris disseminatus faciei is probably best considered as granulomatous rosacea. A variation of rosacea that occurs around the mouth is termed perioral dermatitis. Perioral dermatitis occurs most commonly in adult women, and manifests with erythematous papules around the mouth, but spares the skin around the lips (which then appears pale). Sometimes these papules are associated with papules around the chin, upper lip, and cheeks. Papules can occur around the eyes, in which case the eruption should be described as periocular dermatitis.

Rare associations, forms, and complications of rosacea exist. Haber's syndrome is a genodermatosis, first described in 1965, that manifests on the face as a rosacea-like dermatitis beginning in childhood, followed by pustular flares and photosensitivity. In addition, numerous seborrheic keratoses occur on the trunk. On rare occasions, rosacea fulminans can be associated with Crohn's disease, ulcerative colitis, colon cancer recurrence, and pregnancy. Kaposi's varicelliform eruption can occur in skin affected by rosacea.

Between 6% and 18% of acne rosacea patients have signs or symptoms of ocular rosacea.<sup>15</sup> Rosacea lymphoedema involving the eyelids can

**Figure 2.** Nose of patient with rosacea demonstrating rhinophyma and erythema



light treatments, with intense pulsed light and long-pulsed dye lasers, seem to be effective at decreasing erythema and eliminating telangiectasia, but they are expensive and usually do not permanently eliminate erythema or telangiectasia. Cosmetic camouflage is helpful for patients who do not want treatment or for whom treatment is ineffective. Rosacea remains a challenging entity to treat.

occur. Rosacea keratitis and keratoconjunctivitis sicca can be associated with ocular rosacea.<sup>15</sup>

Rosacea is commonly associated with the topical application of corticosteroids to the face i.e., “steroid rosacea.” It has also been recently linked to the application of tacrolimus and pimecrolimus to the face.

As rosacea has a variety of clinical presentations, it is unsurprising that it also has a variety of histologic presentations. Researchers have stated that no specific histologic features associated with either erythematous-telangiectatic or papulopustular clinical forms of rosacea occur.<sup>16</sup> Another investigator noted that granulomatous rosacea can show mixed lymphohistiocytic inflammation, in one series demonstrating lymphocytic inflammation in 40% of patients, primarily histiocytic with a few giant cells in 34%, epithelioid granulomas in 11%, and epithelioid granulomas with caseation necrosis in 11% of patients.<sup>9</sup> As such, the diagnoses of sarcoidosis, metastatic Crohn’s disease, granuloma annulare, foreign body granuloma, tuberculosis, deep fungal infections, atypical mycobacterial infections, and leprosy enter into the histologic differential diagnosis of granulomatous rosacea. The erythematous papules of rosacea often demonstrate a perivascular and perifollicular infiltrate of lymphocytes and histocytes (activated tissue macrophages), and sometimes multinucleated cells, plasma cells, neutrophils, and eosinophils. The pustules of rosacea can manifest with granulomatous inflammation and perifollicular collections of neutrophils, which can form abscesses. The histologic differential of *Demodex folliculorum* is a common finding in follicles located near the eruption of rosacea.

The range of manifestations and associations of rosacea are suggestive that it is best considered a reaction pattern (perhaps under the general rubric of neutrophilic dermatoses) rather than a unique disease. It seems that the range of etiologies of rosacea include immune defects, inflammatory reaction processes, abnormal vascular reactivity, and

**Table I.** Rosacea Variants, Systemic/Cutaneous Infections Related to Rosacea, and Mimics of Rosacea

Rosacea variants: preferred treatments
Erythematotelangiectatic: light
Papulopustular: antibiotics, retinoic acid, sulfur, topical calcineurin inhibitor
Phymatous: dermabrasion, CO <sub>2</sub> laser
Ocular: eye drops: anti-inflammatory, antibiotic
Systemic/cutaneous infections/colonizations related to rosacea
Sinusitis
<i>Helicobacter pylori</i> infection
<i>Demodex</i> colonization/overgrowth
Mimics of rosacea
Polycythemia vera
Connective tissue diseases (e.g., lupus)
Contact dermatitis
Photosensitivity
Carcinoid
Mastocytosis
Long-term application of topical steroids
Contact dermatitis

**Table II.** Triggers of Rosacea

Foods	Emotion
Cheese (except cottage)	Anger
Chocolate	Stress
Spicy food	Rage
Soy sauce	Embarrassment
Vanilla	Anxiety
Temperature	Drugs
Sauna heat	Niacin
Overheating	Nitroglycerin
Sun lamp	Other vasodilators
Humidity	Activity
Beverages	Exercise
Red wine	Menopause
Hot drinks	Caffeine withdrawal
Alcohol (sometimes)	Chronic cough
Weather	Straining
Sun	Topicals
Heat	Topical corticosteroids
Strong wind	Retinoids
Cold	Cosmetics (sometimes)
	Acetones
	Alcohol

changes in vascular mediating mechanisms that are the reification of aberrant expression of eicosanoids, proinflammatory cytokines, and polymorphonuclear leukocytes.

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Table III. Rosacea Treatments				
APPROVAL STATUS; TYPE		TREATMENT OPTIONS AND PRIORITIES (*/**/†/††)		
FDA APPROVED FOR ACNE OR ROSACEA				
Topical antibiotics	Metronidazole* 0.25%, 0.75%, 1%			
Topical, other	Azelaic acid 15% gel**	Na sulfacetamide 10%/sulfur 5% comb.**	Na sulfacetamide 10%**	Na sulfacetamide 10%/sulfur 5%/ sunblock comb.**
Oral antibiotics	Tetracycline 500 mg b.i.d.*	Doxycycline 50–100 mg b.i.d.*	Minocycline 50–100 mg b.i.d.*	Sub-antimicrobial dose doxycycline 20 mg b.i.d.* or 40 mg q.d.
NOT FDA APPROVED FOR ROSACEA				
Topical antibiotics	Clindamycin 1%**	Erythromycin 2%**	Benzoyl peroxide 5%/clindamycin 1% comb.†	Sunscreen with dimethicone or cyclomethicone†
Topical retinoids	Retinaldehyde 0.05%†	Tretinoin†	Adapalene**	Tazarotene††
Topical, other	Azelaic acid cream 20%**	Crotamiton 10% q.d.–t.i.d.†	Lindane 1% q.d.††	Permethrin cream q.d.–weekly**
	Benzoyl peroxide q.d.–b.i.d.**			
Oral antibiotics	Azithromycin 250 mg t.i.w.–q.d.*	Penicillin 2.4 million U q.d.†	Erythromycin 250–500 mg b.i.d.–q.i.d.*	Amoxicillin/ampicillin 100–500 mg q.d.–b.i.d.†
	Metronidazole 250 mg b.i.d.–t.i.d.**	Clarithromycin 250–500 mg q.d.–b.i.d.**		
Oral, other	Ivermectin 250 µg/kg weekly †	Isotretinoin 0.15–2 mg/kg q.d. × 5–12 mo†	Acitretin 25–50 mg q.d.††	Flaxseed oil, 2 g q.d.†
	Ketoconazole 400 mg q.d. × 1–4 wk†	Spironolactone 50 mg q.d. × 4 wk††	Prednisone 1 mg/kg (rosacea fulminans only)†	
Oral anti-flushing	Oral contraceptives†	Psychiatric medications: amitriptyline 25 mg q.d.†; clonidine 0.1 mg q.d.†; pimozide††	Dapsone (granulomatous rosacea)††	β Blockers†
	Odansetron†			
Topical anti-inflammatory/calceinuric inhibitors	Tacrolimus q.d.–b.i.d.**‡	Pimecrolimus q.d.–b.i.d.**‡		
Phototherapy (expensive and not permanent)	Intense pulsed light (IPL) therapy†	Photodynamic therapy with IPL, preceded by application of topical aminolevulinic acid†	585/595-nm Short-pulsed dye laser; purpura induction and new long-pulsed lasers better††	K-titanyl-phosphate lasers and diode-pumped frequency-doubled lasers (532 nm)††
	585/595-nm Long-pulsed dye laser†	Electrosurgery for fine blood vessels†		
Surgery/rhinophyma	Dermabrasion†	CO <sub>2</sub> laser†	Surgical shave techniques†	Chemical peel†
	Cryotherapy†	Shaw scalpel†	Argon laser††	
Herbal	Green tea	Feverfew, lavender	Camphor oil	Tea tree oil
	Licorice	Chamomile	Oatmeal	

FDA=US Food and Drug Administration; comb.=combination; \*first-line; \*\*second-line; †third-line; ††fourth-line (disfavored if other options exist); ‡based on effectiveness (good), cost (very high), and not accounting for black box warnings and medicolegal issues

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