

CLINICAL PRACTICE

Rosacea

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 47-year-old white woman reports facial redness and flushing. Her eyes are itchy and irritated. She thinks she may have rosacea and is worried that she will have a "whiskey nose." On examination, multiple erythematous papules, pustules, and telangiectasias are observed on a background of erythema of the central portion of her face. How should her case be managed?

THE CLINICAL PROBLEM

A constellation of clinical symptoms and signs are included under the broad rubric of rosacea. These consist of facial flushing, the appearance of telangiectatic vessels and persistent redness of the face, eruption of inflammatory papules and pustules on the central facial convexities, and hypertrophy of the sebaceous glands of the nose, with fibrosis (rhinophyma).¹ Ocular changes are present in more than 50 percent of patients and range from mild dryness and irritation with blepharitis and conjunctivitis (common symptoms) to sight-threatening keratitis (rare).² Patients with rosacea may report increased sensitivity of the facial skin³ and may have dry, flaking facial dermatitis, edema of the upper face,⁴ or persistent granulomatous papulonodules.⁵ There is often an overlapping of clinical features, but in the majority of patients, a particular manifestation of rosacea dominates the clinical picture. As a useful approach to the guidance of therapy, the disease can thus be classified into four subtypes — erythematotelangiectatic (subtype 1), papulopustular (2), phymatous (3), and ocular (4)⁶ — with the severity of each subtype graded as 1 (mild), 2 (moderate), or 3 (severe).⁷ The psychological, social, and occupational effects of the disease on the patient should also be assessed and factored into treatment decisions.

The onset of rosacea usually occurs between the ages of 30 and 50 years.⁸ The course of the disease is typically chronic, with remissions and relapses. Some patients identify exacerbating factors, particularly in regard to flushing, such as heat, alcohol, sunlight, hot beverages, stress, menstruation, certain medications, and certain foods.⁹ Rosacea is more common in women than in men, but men with rosacea are more prone to the development of thickening and distorting phymatous skin changes. Rosacea has been anecdotally reported to be associated with seborrheic dermatitis (this association is likely), with migraine headaches in women¹⁰ (possible), and with *Helicobacter pylori* infection¹¹ (controversial). A rosacea-like eruption can be induced by the topical application of fluorinated corticosteroids¹² and tacrolimus ointment¹³ to the face. In two European population studies, the prevalence of rosacea was reported to be 1.5 percent¹⁴ and 10 percent,¹⁵ but estimates are complicated by the difficulty of distinguishing between chronic actinic damage and erythematotelangiectatic rosacea. Although rosacea can occur in all racial and ethnic groups, white persons of Celtic origin are thought to be particularly prone to the disorder,¹⁶ and it is uncommon in persons with dark skin. Up to 30 percent of patients report a family history of rosacea.¹⁷ The common misconception

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<p>Ocular (subtype 4)</p>	<p>Sensation of foreign body in the eye; telangiectasia and erythema of lid margins, often with scaling. Conjunctival injection; recurrent chalazion or hordeolum. Keratitis, episcleritis or scleritis; and iritis may occur, though rarely. May precede, follow, or occur simultaneously with cutaneous changes. Both eyes are usually affected.</p>	<p>1 Mild itch, dryness, or grittiness of eyes; fine scaling of lid margins; telangiectasia and erythema of lid margins; mild conjunctival injection (mild congestion of conjunctival vessels).</p> <p>2 Burning or stinging of eyes; crusting or irregularity of lid margins, with erythema and edema; definite conjunctival hyperemia or injection; formation of chalazion or hordeolum.</p> <p>3 Pain, photosensitivity, or blurred vision; severe lid changes, with loss of lashes; severe conjunctival inflammation; corneal changes, with potential loss of vision; episcleritis or scleritis; iritis.</p>	<p>Topical medication for grade 1; systemic medication for grade 2. Refer patients with persistent grade 1 or 2 disease or suspected grade 3 disease to ophthalmologist.</p>	<p>May occur in the majority of rosacea cases, but often not diagnosed. Vision-threatening ocular inflammation is rare.</p>
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* Adapted from Wilkin et al.^{6,7}

† In general, 1 denotes mild disease, 2 moderate disease, and 3 severe disease, but grades of severity are not always clearly defined. Patients may have more than one subtype, and the grade of severity should be assessed in each of these. Patients should also be asked to grade the psychological, social, and occupational effects of their disease on a similar scale. For example, in grade 1 (mild), the patient is conscious of the condition, but it does not cause embarrassment or inhibit social functioning; in grade 2 (moderate), the patient is constantly aware of the rosacea during social situations and it regularly causes embarrassment; in grade 3 (severe), the patient is constantly thinking about the condition and avoids social interaction because of it. Such grading on the part of the patient facilitates evaluation of the overall effect of the disease on him or her and guides assessment of the efficacy of therapy.

that both the facial redness and the rhinophyma associated with rosacea are due to excessive alcohol consumption makes rosacea a socially stigmatizing condition for many patients.

STRATEGIES AND EVIDENCE

The diagnosis of rosacea is a clinical one. There is no confirmatory laboratory test. Biopsy is warranted only to rule out alternative diagnoses, since histopathological findings are not diagnostic.¹⁸

The differential diagnosis and therapy vary according to subtype (Table 1). Rosacea that is manifested predominantly by flushing is difficult to treat, but the condition may improve with the management of other manifestations and the avoidance of provoking or triggering factors. Inflammatory changes in the skin are usually responsive to medical therapies and heal without scarring, whereas telangiectasias and phymatous changes often require laser or surgical intervention. Ocular rosacea is usually mild and responsive to lid hygiene, tear replacement, and topical or systemic antibiotics, but patients with persistent or severe ocular disease should be referred to an ophthalmologist. All patients should be advised in regard to protection from climatic influences (both heat and cold), avoidance of factors that trigger or exacerbate flushing or that irritate the often-sensitive skin, appropriate care of the facial skin (Table 2), and a strategy for maintenance of remission when the condition improves. The choice of medications, dosages, and duration of therapy is often based on clinical experience. Off-label prescription-drug use is common.¹⁹

SUBTYPE 1

Flushing, with persistent central facial erythema (erythematotelangiectatic rosacea), is probably the most common presentation of rosacea.⁶ Although it has been suggested that rosacea is essentially a cutaneous vascular disorder,²⁰ facial flushing is not always a feature; patients who report flushing as their only symptom should not receive a diagnosis of "prerosacea," since, in many such patients, rosacea never develops. Common causes of flushing (e.g., psychosocial factors or anxiety, food, alcohol or drugs, or menopause) should become apparent when a medical history is taken. Prolonged episodes of severe flushing accompanied by sweating, flushing that is not limited to the face, and, especially, systemic symptoms such as diarrhea, wheezing, headache, palpitations, or weakness indicate the need

convexities of the central portion of the face, with background erythema (Fig. 2), typify papulopustular rosacea.⁶ In grade 3 disease, plaques can form from the coalescence of inflammatory lesions (Fig. 3). Telangiectatic vessels, varying degrees of edema, ocular inflammation, and a tendency to flush are present in some patients. The differential diagnosis includes acne vulgaris, perioral dermatitis, and seborrheic dermatitis. Patients with acne vulgaris have less erythema, are often younger, and have oily skin with blackheads and whiteheads (comedones), larger pustules and nodulocystic lesions, and a tendency to scarring. In patients with perioral dermatitis, micropustules and microvesicles around the mouth or eyes and dry, sensitive skin may follow the inappropriate use of topical corticosteroids. Seborrheic dermatitis may accompany rosacea and contribute to the facial erythema, but it is distinguished from rosacea by a prominence of yellowish scaling around the eyebrows and alae nasi, together with troublesome dandruff.

Management

Systemic or topical antibiotics, or both, are the mainstays of therapy for subtype 2 rosacea (Table 3), and the response is often satisfactory (Fig. 4A and 4B). Moderate-to-severe (i.e., grade 2 or 3) papulopustular rosacea may require systemic therapy to achieve clearance of inflammatory skin lesions, whereas milder (grade 1 and some cases of grade 2) disease can often be treated with topical medications alone.²⁵ Although data are lacking to support the combined use of topical and systemic therapies, many clinicians recommend such a combination for the treatment of moderate-to-severe disease.^{20,25}

On the basis of an analysis that pooled data from two randomized trials, van Zuuren and colleagues concluded that there was strong evidence of the efficacy of topical metronidazole and azelaic acid cream.²⁶ Sixty-eight of 90 patients (76 percent) treated with topical metronidazole for eight or nine weeks considered their rosacea to be improved, as compared with 32 of 84 patients (38 percent) in the placebo group.²⁶ Significant reductions in the number of inflammatory lesions and in erythema were reported in two large placebo-controlled, double-blind studies of a 15 percent azelaic acid gel applied twice daily.²⁷ A double-blind, randomized, parallel-group trial involving 251 patients with papulopustular rosacea²⁸ demonstrated the superiority of 15 percent azelaic acid gel over 0.75 percent metronidazole gel applied twice daily for 15 weeks. In a dou-



Figure 2. Papulopustular (Subtype 2) and Ocular (Subtype 4) Rosacea of Moderate Severity.

In this example of grade-2-to-3 disease, the typical distribution of papules and pustules on a background of inflammatory erythema is seen over the convexities of the central portion of the face, with sparing of the periocular area. Grade-1-to-2 ocular rosacea (erythema and edema of the upper eyelids) is also present.

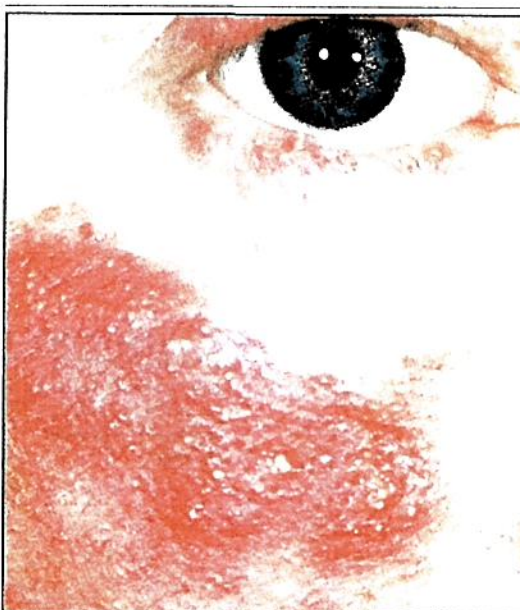


Figure 3. Severe Papulopustular Rosacea with Moderate Ocular Involvement.

In this patient with grade 3 papulopustular disease, inflammatory lesions have coalesced into an erythematous plaque below the eye. Note the multiple small, studded pustules on the surface of the plaque and the inflammatory lesions on the lower eyelid (grade 2 ocular rosacea).

Medication	Properties and Actions	Dosage and Duration†	Contraindications and Side Effects‡	Comments
Doxycycline	Antibacterial; antiinflammatory.	50 to 100 mg once or twice daily for 6 to 12 weeks.	Same as for oxytetracycline.	May be taken with food.
Minocycline	Antibacterial; antiinflammatory.	50 to 100 mg twice daily or sustained-action formulation once daily for 6 to 12 weeks.	Contraindications: pregnancy or lactation. Persons with hepatic impairment should use with caution. Side effects: gastrointestinal upset (but less than with tetracycline); allergic reactions. Hyperpigmentation of the skin may occur. Long-term use should be avoided (hepatic damage or systemic-lupus-erythematosus-like syndrome may be induced). Drug interactions with antacids, mineral supplements, anticoagulants.	Randomized, clinical trials to support its use in rosacea are lacking, but clinical impression is of equal efficacy to oxytetracycline. Unlike oxytetracycline, can be taken with food.
Erythromycin	Antibacterial; antiinflammatory.	250 to 500 mg once or twice daily for 6 to 12 weeks.	Contraindications: severe hepatic impairment. Side effects: gastrointestinal upset; headache or rash. Drug interactions (many).	Alternative to oxytetracycline or minocycline as first-line systemic treatment. Useful if systemic therapy necessary in oxytetracycline-intolerant or pregnant or lactating patients.
Metronidazole	Antibacterial; antiinflammatory.	200 mg once or twice daily for 4 to 6 weeks.	Contraindications: pregnant or lactating women should use with caution. Side effects: gastrointestinal upset; leukopenia; neurologic effect (seizures or peripheral neuropathy). Drug interactions with alcohol, anticoagulants, or phenobarbital.	Side-effect profile limits its use to resistant cases for short periods.

* Topical treatment alone is usually effective for mild-to-moderate (grade-1-to-2) papulopustular rosacea. Topical metronidazole, combination 10 percent sodium sulfacetamide and 5 percent sulfur, and 15 percent azelaic acid have been approved by the Food and Drug Administration for the treatment of rosacea; however, several other topical medications are used off label. For patients with moderate-to-severe papulopustular rosacea (grade 2 to 3), oral medication is usually indicated. These patients may not tolerate topical medications initially, owing to inflamed skin, but topical therapy may be added as the inflammation subsides and is used to maintain remission after cessation of oral therapy.

† Dosage ranges relate to published reports and reflect the lack of uniformity in the approach to the treatment of papulopustular rosacea.

‡ Contraindications and side effects are selected examples rather than a comprehensive summary.

ble-blind study of 103 patients, a lotion containing 10 percent sodium sulfacetamide and 5 percent sulfur reduced inflammatory lesions by 78 percent, as compared with a reduction of 36 percent in the placebo group.²⁹ An investigator-blinded study involving 63 patients that compared the combination of 10 percent sodium sulfacetamide and 5 percent sul-

fur lotion with 0.75 percent metronidazole showed a significantly greater clearance of lesions among the patients treated with sodium sulfacetamide and sulfur.³⁰ An uncontrolled study showed a reduction in erythema, papules, and pustules in 13 of 15 patients (87 percent) who were treated with topical erythromycin applied twice daily for four weeks.³¹



Figure 5. Advanced Rhinophyma (Subtype 3).

In grade 3 rhinophyma, enlargement and distortion of the nose occur, with prominent pores and thickened skin due to hyperplasia of the sebaceous glands and fibrosis of the connective tissue. There is follicular prominence and a distorted nodular appearance. In this patient, the rhinophyma was accompanied by mild papulopustular rosacea, which responded well to topical medications.

guish atypical, or nodular, rhinophyma from lupus pernio (sarcoidosis of the nose); basal-cell, squamous-cell, and sebaceous carcinomas; angiosarcoma; and even nasal lymphoma.⁴⁵

Data from randomized trials of therapies for rhinophyma and long-term follow-up studies of recurrence rates are lacking. Clinical experience suggests that grades 2 and 3 rhinophyma respond well, at least initially, to surgical excision, electrosurgery, or carbon dioxide–laser therapy. A case series of 30 patients who were treated with carbon dioxide lasers and followed for one to three years showed good cosmetic results in almost all the patients.⁴⁶

SUBTYPE 4

Ocular rosacea is common but often not recognized by the clinician.⁴⁷ It may precede, follow, or occur simultaneously with the skin changes typical of rosacea. In the absence of accompanying skin changes, ocular rosacea can be difficult to diagnose, and there is no test that will confirm the diagnosis. Patients usually have mild, nonspecific symptoms, such as burning or stinging of the eyes. A sensation of dryness is common, and tear secretion is frequently decreased.⁴⁸ Mild-to-moderate ocular rosacea (including blepharoconjunctivitis, chalazia, and hordeola) occurs frequently, whereas serious (grade 3) disease with the potential for visual loss, such as that which results from keratitis, occurs rarely.

Artificial tears, eyelid hygiene (i.e., cleaning the

lids with warm water twice daily), fucidic acid, and metronidazole gel applied to lid margins are treatments that are frequently used to treat mild ocular rosacea. Systemic antibiotics are often additionally required for grade-2-to-3 disease, although limited data are available to support these approaches. In a double-blind, placebo-controlled trial, 35 patients with ocular rosacea who received 250 mg of oxytetracycline twice daily for six weeks had a significantly higher rate of remission than did patients who received a placebo (65 percent vs. 28 percent).⁴⁹ In an uncontrolled study of 39 patients with cutaneous rosacea (28 with ocular symptoms), 100 mg of doxycycline daily for 12 weeks improved symptoms of dryness, itching, blurred vision, and photosensitivity.⁵⁰ After ocular symptoms subside, the maintenance of lid hygiene and the use of artificial tears are usually recommended. However, such treatment may be inadequate for moderate-to-severe ocular rosacea, and patients with persistent or potentially serious ocular symptoms should be referred to an ophthalmologist.

AREAS OF UNCERTAINTY

The causes and pathogenesis of rosacea remain poorly understood.^{4,51} Data from randomized, clinical trials on the efficacy and optimal duration of many of the therapies, including complementary therapies that are frequently used by patients,⁵² are lacking. The possibility of emergence and carriage on the skin of resistant organisms is a concern with regard to the prolonged use of topical and systemic antibiotics.

GUIDELINES

There are no specific guidelines for the management of rosacea.

SUMMARY OF RECOMMENDATIONS

“Rosacea” is a diagnostic term applied to a spectrum of changes in the skin and eyes. Until the causes and pathogenesis are better understood, the classification of rosacea by its predominant features and grading according to severity (Table 1) are recommended to guide management. The emotional effect of rosacea on the patient must also be considered in the management of this condition, and advice on improving the cosmetic appearance of the skin is an important aspect of overall care.

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CLINICAL TRIAL REGISTRATION

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