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Rosacea is a common, but frequently misunderstood, skin condition. As it affects the face and is unsightly, rosacea can cause considerable social distress, especially because of the historical belief that alcohol is involved in its causation. This article outlines the clinical features of rosacea and the standard subtype classification of the condition. The theories of pathogenesis are outlined and the management approaches are discussed.

Key words: rosacea, classification, rhinophyma, ocular disease, management

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Introduction

Rosacea is a chronic recurrent inflammatory dermatosis primarily affecting the central areas of the face and is characterized by varying degrees of facial redness (erythema), inflammatory lesions (papules and pustules), puffiness (edema), a high colour and broken blood vessels (telangiectasias), enlargement of the nose (rhinophyma), discomfort or inflammation of the eyes (ocular rosacea), and a propensity to flush.¹ Ocular involvement occurs in over 50% of patients.²

Rosacea is relatively common and is estimated to affect up to 14 million people in the United States.³ The prevalence of rosacea is highest among fair-skinned individuals, especially those of Celtic origin, and is uncommon in darkskinned individuals.¹

The onset of rosacea in the majority of patients is between thirty and sixty years of age, and the disease continues to remit and relapse for many years into old age. It affects more women than men. However, males more frequently develop rhinophyma, the swelling and distortion of the nose due to sebaceous gland and connective tissue hyperplasia. Rosacea has been reported to be associated with seborrheic dermatitis, migraine headaches in women, and possibly *H. pylori* infection of the stomach.¹ A rosaceiform eruption can be induced by the topical application of fluorinated cortico-steroids and tacrolimus ointment.¹

Like all facial eruptions, rosacea has a significant psychosocial impact and therefore a sympathetic approach by the physician to the diagnosis and management of this condition is critical. The common misconception that rosacea may be linked with alcohol misuse means this condition can be particularly socially distressing for the sufferer. An association between rosacea and depression has been suggested in one study.¹⁸

Clinical Features

Symptoms and signs of rosacea include facial flushing, persistent centrofacial erythema, inflammatory papules and pustules, telangiectatic vessels, and hypertrophy of the sebaceous glands with fibrosis. Ocular changes can range from mild blepharitis and conjunctivitis through to sight-threatening keratitis.² Typically, rosacea follows a pattern of remission and exacerbation. While there is often an overlap of clinical features, in the majority of patients a particular aspect of the clinical presentation of rosacea dominates. This allows clinicians to classify rosacea into four subtypes: erythematotelangiectatic (subtype 1), papulopustular (subtype 2), phymatous (subtype 3), and ocular (subtype 4) (Table 1).⁴ The severity of each subtype can be graded as 1 (mild), 2 (moderate), or 3 (severe).⁴ The significance of classifying rosacea relates to the selection of appropriate therapy.

Diagnosis and Differential Diagnoses

The diagnosis of rosacea is based on the clinical features (Table 1). There is no laboratory test (including histological

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Figure 1a: Erythematotelangiectatic rosacea



examination of affected skin biopsy material) that will confirm the diagnosis. Tests are usually undertaken to exclude alternative conditions (e.g., skin biopsy, antibody screens) (Table 2). The clinical presentation of rosacea is discussed under the four classified subtypes.

Clinical Presentation Subtype 1

Patients with erythematotelangiectatic rosacea often complain of troublesome flushing and have persistent central facial erythema. Telangiectatic vessels may be present (Figure 1a). Flushing is exacerbated by spicy foods, alcohol, hot drinks, temperature change, exercise, and emotional stress.^{1,4} Patients with erythematotelangiectatic rosacea have a lower threshold for irritation from topically applied substances, and

Figure 1b: Lupus erythematosis

they experience stinging, burning, or itch.¹ Erythematotelangiectatic rosacea can be difficult to differentiate from the effects of chronic actinic damage on facial skin, and the two conditions may coexist. As the management of both these conditions is similar, their distinction is not critical for patient care but is obviously important when studying the pathogenesis or epidemiology of rosacea. Occasionally, the erythema of erythematotelangiectatic rosacea can appear similar to the facial butterfly rash of lupus erythematosis (Figure 1b).^{1,4} In this setting, skin biopsy, serology testing for antinuclear and anticytoplasmic antibodies, or other investigations may be necessary. Prolonged episodes of severe flushing associated with sweating, generalized flushing, or systemic symptoms such as diarrhea, wheeze, headache, palpitations, or weakness indicate the need for investigations to rule out

Table 1: Subtype Features and Differential Diagnosis				
Subtype	Features	Differential Diagnosis to Be Considered		
1. Erythematotelangiectatic	Flushing, persistent central facial erythema; telangiectatic vessels; easily irritated skin	Chronic actinic damage; lupus erythematosis; carcinoid; phaeochromocytoma; mastocytosis; dermatomyositis		
2. Papulopustular	Persistent facial erythema; erythematous papules surmounted by pustules; edema Other possible features: flushing, telangiectasias, ocular inflammation, phymatous skin changes	Acne vulgaris; perioral dermatitis; seborrheic dermatitis		
3. Phymatous	Distorted, thickened skin with prominent pores; surface nodules	lupus pernio; basal cell carcinoma; squamous cell carcinoma; angiosarcoma; nasal lymphoma		
4. Ocular	Itch, irritation, burning, stinging, watering, dryness, blurred vision Also: telangiectasia and erythema of the lid margins; Conjunctival injection; chalazion (i.e., a stye: a localized infection of the eyelid margin); hordeolum (a granuloma of a meibomian gland); interstitial keratitis; episcleritis; scleritis; iritis	Staphylococcal blepharitis; seborrheic blepharitis; other causes of keratitis and scleritis		

Table 1: Subtype Features and Differential Diagnosis

systemic diseases such as carcinoid syndrome, phaeochromocytoma, or mastocytosis (Table 2). 1

Subtype 2

Papulopustular rosacea (acne rosacea) is characterized by small erythematous papules that may be surmounted by small pustules and which occur on the central face on a background of inflammatory erythema (Figure 2a).⁴ The inflammation can lead to chronic edema. In grade 3 disease, plaques can form from the coalescence of inflammatory lesions.¹ Patients with papulopustular rosacea may also have features of erythematotelangiectatic rosacea (i.e., a tendency to flush easily and telangiectatic vessels on the face).

The differential diagnosis of papulopustular rosacea includes acne vulgaris, perioral dermatitis, and seborrheic dermatitis.¹ Patients with acne vulgaris tend to be younger

and, unlike rosacea patients, have comedones (whiteheads and blackheads) and a tendency towards scarring of the skin.¹ Patients with perioral dermatitis have micropustules and microvesicles around the mouth or eyes (Figure 2b).⁴ Seborrheic dermatitis can accompany rosacea in many patients; however, it is a distinctive dermatosis and it can be distinguished from rosacea by the presence of yellow scaling around the eyebrows and alae nasi (the rounded eminence of the lateral external nose) in association with dandruff of the scalp.¹ It may contribute to the facial erythema, particularly on the forehead. Male patients with seborrheic dermatitis may have similar redness and scaling of the anterior chest.

Subtype 3

Phymatous rosacea is rare and most commonly seen in men. It results from hyperplasia of the sebaceous glands and con-

Table 2: Investigations to Be Considered			
Differential Diagnosis Considered in Erythematotelangiectatic Rosacea	Investigations		
Lupus Erythematosis	Antinuclear antibodies including double-stranded DNA, antiphospholipid, antinuclear and antismith antibodies; syphilis serology; complement; Coombs test; histopathological examination		
Carcinoid Syndrome	24-h urine excretion of 5-hydroxyindoleacetic acid (HIAA) Whole blood serotonin concentration Epinephrine or pentagastrin provocation test Localizing abdominal CT or pentetreotide imaging		
Phaeochromocytoma	Plasma or urine catecholamine and metanephrine secretion Clonidine suppression test CT or MRI scan MIGB scintigraphy (123-1-metaiodobenzylguanidine)		
Mastocytosis	Serum tryptase 24-h urinary histamine Bone marrow biopsy Histopathological examination of extramedullary organs Radiological imaging +/- gastrointestinal investigations		
Dermatomyositis	Serum muscle enzymes Serum autoantibodies Electromyography Muscle biopsy		
Lupus Pernio – Sarcoidosis	Serum calcium; serum angiotensin converting enzyme (ACE) Histopathological examination Chest X-ray Pulmonary function tests Bronchoalveolar lavage		

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Figure 2a: Papulopustular rosacea

Figure 2b: Perioral Dermatitis



nective tissue and is characterized by distorted, thickened skin and surface nodules. It is most commonly seen on the nose (rhinophyma) but can also occur on the chin (gnathophyma), forehead (metophyma), one or both ears (otophyma), and eyelids (blepharophyma).⁴ Phymatous changes can occur with minimal or no other changes of rosacea.¹ In the early stages of rhinophyma there is swelling of the nose, and the sebaceous gland hyperplasia gives rise to accentuation of the follicular openings, giving a "peau d'orange" appearance (Figure 3a). In some cases, when the rhinophyma is nodular or atypical, differential diagnoses such as lupus pernio (sarcoidosis of the nose which has a shiny violaceous appearance and lacks the peau d'orange appearance of rosacea)(Figure 3b); basal cell, squamous cell, and sebaceous carcinomas; angiosarcoma; and, rarely, nasal lymphoma may need to be considered.¹ A biopsy may be necessary to exclude these conditions in atypical cases of rhinophyma.

Subtype 4

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Ocular inflammation occurs in approximately 50% of patients with rosacea but is frequently overlooked.² Symptoms are

Figure 3a: Rhinophyma

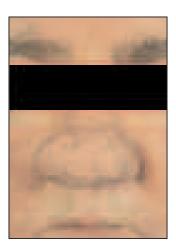


Figure 3b: Lupus Pernio (sarcoidosis)



usually mild itch, irritation, burning, stinging, watering, and dryness. Rarely, symptoms can be severe with pain and blurred vision. Blepharoconjunctivitis, chalazia, and hordeola are common findings, whereas keratitis is rare.⁵ Interstitial keratitis is thought to be specific for rosacea, but all other eye signs are nonspecific.⁵ Ocular rosacea may precede the cutaneous signs; however, concomitant or eye findings following the skin signs are more often observed.¹ The diagnosis of ocular rosacea in the absence of accompanying skin lesions is problematic, as the ocular symptoms and signs are nonspecific and can occur for other reasons (Table1).⁵

Etiology

The cause of rosacea has not been established. Genetic and environmental factors are thought to have an impact on the pathogenesis as up to 30% of patients report a family history of rosacea. Solar damage to facial skin is a consistent finding in biopsies of affected skin, and most patients have types I or II fair sun-sensitive skin. Several possible etiologic theories have been suggested to explain the facial erythema and inflammatory lesions including abnormalities in the vascular system of the face,³ immune system,⁴ and antioxidant system.⁶ Microorganisms such as the Demodex mite (which is found in increased numbers in the facial skin)^{3,4} and bacteria⁷ have also been considered to potentially play a role. The cause of rosacea may well be multifactorial (Table 3).

Histopathology

The histopathological changes seen in the skin in rosacea, shown in Figure 4, are not diagnostic. Solar elastosis (damage to the collagen in the dermis) is uniformly present in facial skin biopsies of rosacea patients. Telangiectasia are reflected by the presence of dilated superficial dermal vessels that may or may not have a mild surrounding inflammatory infiltrate, the extent and pattern of inflammation of which is variable. In erythematotelangiectatic cases there may be a mild perivascular lymphohistiocytic infiltrate. In papular rosacea the infiltrate is more intense in a perifollicular distribution, often with an admixture of neutrophils. Pustules are seen as a polymorphonuclear neutrophil accumulation in the follicular wall and upper part of the pilosebaceous follicle. Granuloma formation is sometimes observed, usually in association with adjacent damaged follicles.^{38,9}

Management A) General Measures

All patients with rosacea should be guided toward general nonpharmacologic measures to avoid triggering or exacerbating their condition. Patients should attempt to identify aggravating factors for flushing and avoid these.¹⁰ Patients with rosacea have easily irritated skin, so mild cleansers and emollients are advised. All patients with rosacea should apply sunscreens daily to prevent the development of facial photodamage that will exacerbate the redness of rosacea.¹¹ Silicone

Figure 4: Histopathology of Rosacea

solar elastosis

damage to the collagen in the dermis is uniformly present in facial skin biopsies of rosacea patients.

perivascular lymphohistiocytic infiltrate can be seen in erythematotelangiectatic cases of rosacea.

papular rosacea an intense

lymphohistiocytic infiltrate can be seen in a perifollicular distribution, often with an admixture of neutrophils.

telangiectasia

are reflected by the presence of dilated superficial dermal vessels that may or may not have a mild surrounding inflammatory infiltrate.

pustules

are seen as a polymorphonuclear neutrophil accumulation in the follicular wall and upper part of the pilosebaceous follicle. Granuloma formation is sometimes observed.

Table 3: Postulated Etiologic Factors in Rosacea				
Etiologic Factor	Comment			
Type I or II fair skin/actinic damage	Actinic damage causes persistent erythema and telangiectasias. Sun exposure may precipitate acute episodes of flushing. UV exposure induces abnormalities of the dermal connective tissue, which may alter lymphatic and blood vessel function. ⁴			
Abnormalities of the cutaneous vascular homeostasis	Result in vasodilation and frequent flushing ⁴			
Temperature sensitive bacteria	Rosacea skin is warmer than normal, which may alter the nature and behaviour of bacteria. ⁷ At higher temperatures, coagulase-negative staphylococci make and secrete proteins that contribute to inflammation and subsequent papules, pustules, and dermatitis.			
Demodex folliculorum and Demodex brevis (hair follicle mites)	Rosacea patients have an increased density of Demodex mites. Demodex may trigger a hypersensitivity reaction that contributes to papule and pustule formation. Mites may carry bacteria that initiate inflammation. ^{8,14}			
Decreased antioxidant protection	The skin uses antioxidant to protect itself from photodamage. Antioxidant protection may be decreased in rosacea patients. ⁶			
Helicobacter pylori infection of the gastrointestinal tract	No robust evidence to support this theory. It must be considered that <i>H. pylori</i> infection is common and is treated with antibiotics. ⁴			

sunscreens and physical sun block, such as titanium or zinc oxide, are better tolerated than chemical sunscreens by the sensitive skin of rosacea patients.¹¹ Advice on effective cosmetic coverage of rosacea can be given. The application of a green-tinted cosmetic cover-up product can neutralize facial erythema and enhance the camouflaging action of facial foundations.¹ Medications that can exacerbate flushing should be avoided where possible. These include vasodilating drugs, nicotinic acid, calcium channel blockers, and opiates. Patients should be reassured regarding the benign nature of the condition and the possibility of controlling it with appropriate management. They should be informed of the rarity of rhinophyma, which many patients dread. Patients can be directed to groups such as the National Rosacea Society (www.rosacea.org) and the American Academy of Dermatology (www.aad.org) for accurate and appropriate information (Table 4).

B) Specific Treatment Is Guided by the Subtype of Rosacea

Subtype 1 or erythematotelangiectatic rosacea is difficult to treat. Facial erythema is often persistent despite appropriate management. Physicians should discuss this treatment challenge with patients to ensure that they have informed expectations. The general measures outlined are particularly important for patients with this subtype of rosacea. Where telangiectatic vessels are significant, pulsed dye laser therapy, which causes selective photothermolysis, can be employed. It targets chromophores in the red spectrum and

Table 4: General Nonpharmacologic Guidelines for the Management of Rosacea

Reassure patients about the benign nature of the disorder and the rarity of rhinophyma.

Direct patients to web sites such as the National Rosacea Society (www.rosacea.org) and the American Academy of Dermatology (www.aad.org) where accurate information can be accessed.

Advise patients to keep a daily diary to identify precipitating factors with regard to flushing, and then to avoid these exacerbating factors.

Suggest a daily application of sunscreen.

Inform the patients about cosmetic coverage: use of a brush application of facial foundations and the application of matte finish, water-soluble facial powder containing inert green pigments that assist in neutralizing erythema.

Source: Adapted from Powell FC, 2005.1

Table 5: Treatment for Rosacea Subtypes Subtype **Therapeutic Approach** Comments 1. Erythematotelangiectatic Reduce facial erythema and minimize flushing Difficult to treat satisfactorily Topical medications are not recommended as they can cause irritation Ablative therapy for grade prominent vessels 2. Papulopustular Response is usually good; maintenance Topical or systemic medications for grade 1-2 disease Topical and systemic medications for grade 3 therapy is usually required to remain a remission 3. Phymatous Mild changes may improve with treatment of Phymatous skin changes are rare inflammatory lesions It is more common in men Rhinophyma may respond to surgical or laser therapy Other phymatous changes are very difficult to treat 4. Ocular General measures e.g., lid hygiene May occur in the majority Topical medications for grade 1; systemic medications of cases but is often undiagnosed Vision-threatening ocular inflammation for grade 2; referral to ophthalmology for severe or persistent symptoms is rare

Source: Adapted from Powell FC, 2005.¹

Table 6: Medications Used to Treat Papulopustular Rosacea				
Topical Treatments	Metronidazole (0.75% gel or cream; 1% cream)	Applied once or twice daily Can be used as initial treatment or as maintenance therapy		
	Azelaic acid (20% cream; 15% gel)	Applied twice daily Can be used as initial treatment or as maintenance therapy		
	10% Sodium sulfacetamide and 5% Sulfur in cream or lotion Preparations may include 10% urea; sunscreen; green tint	Applied twice daily Can be used as initial treatment or as maintenance therapy		
	Erythromycin (2% solution)	Applied twice daily Can be used as initial treatment or as maintenance therapy		
Systemic Treatment	Oxytetracycline	250–500 mg twice daily for 6–12 weeks to achieve remission. Intermittent low-dose therapy may prevent relapse		
	Doxycycline	50–100 mg once or twice daily for 6–12 weeks		
	Minocycline	50–100 mg twice daily or sustained-action formulation once daily for 6–12 weeks		
	Erythromycin	250–500 mg once or twice daily for 6–12 weeks		
Source: Adapted from Powell FC, 2005. ¹				

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results in coagulation of the superficial vessels without associated dermal damage. $^{1\!1}$

Topical and systemic antibiotics are the principal treatments for subtype 2 or papulopustular rosacea. Mild disease (grade 1) can often be managed with topical therapies alone.¹ The efficacy and tolerability of topical metronidazole has been demonstrated in several randomized, placebo-controlled trials, where a 48–65% reduction in the number of papules and pustules was shown following 7–12 weeks of treatment with topical metronidazole. The antibiotic was also more effective than placebo in maintaining a remission in patients with rosacea.¹⁰

Sodium sulfacetamide (sulphonamide with antibacterial activity) and sulfur (keratolytic) is useful as a solitary topical treatment or as an adjunct therapy.¹ Some preparations additionally contain sun-blocking agents and tinted colour to mask erythema.¹ Topical azelaic acid is comparable in efficacy to topical metronidazole.^{10,11} Its action is attributed to antibacterial and anti-inflammatory activity as well as normalization of keratinization. Topical erythromycin (antibacterial; anti-inflammatory) is another effective therapy.^{10,11} Systemic agents, with or without concurrent topical treatment, are indicated in moderate to severe (grades 2 and 3) papulopustular rosacea. Oxytetracycline, doxycycline, erythromycin, and minocycline are most frequently used.¹ Generally, conventional doses are prescribed to treat rosacea, although recent evidence suggests low-dose therapy may be as effective.^{12,13} Treatment should continue for 4–12 weeks. Patients often relapse within weeks of ceasing systemic treatments. Accordingly, continued use of topical therapy is advised to maintain a remission.¹⁰

Subtype 3 or phymatous rosacea is uncommon. Rhinophyma is the only form of phymatous rosacea that is amenable to treatment. Grades 2 and 3 rhinophyma can be effectively treated with dermabrasion, surgical excision, electrosurgery, or CO2–laser therapy. A combination of therapies may provide the best results.¹

Ocular rosacea (subtype 4) is common and usually mild. It is treated with good eyelid hygiene (cleansing with warm water with a few drops of baby shampoo added), warm compresses, artificial tears, and topical application of metronidazole gel to the eyelid margins.² Grades 2 and 3 may require treatment with systemic antibiotics. Referral to an ophthalmologist should be made if symptoms are persistent or severe.¹

Treatments for the various subtypes are summarized in Tables 5 and 6.

Rosacea in the Older Patient

Although there are no studies to confirm this, the clinical impression of the authors is that rosacea tends to be less common in patients beyond the upper limit of age of onset (>60). The reason for this is unclear, but may reflect a reduced immune reactivity to bacterial or other antigens in this older age group. Treatment of older patients is similar to that of other ages, but clear instructions (verbal and written) with regard to administration of the treatments is particularly important with these patients in view of the possibility of cognitive decline. The older patient's skin can be more sensitive to topical treatments, so caution should be exercised when prescribing potentially irritating preparations. The clinician should be cognizant of the potential

Key Points

Rosacea is a common condition with a significant psychosocial impact.

Rosacea can be classified into subtypes that guide effective therapy.

All patients should apply sunscreen daily and, where possible, avoid exacerbating factors.

Erythematotelangiectatic rosacea is best managed with sun protection and possibly carbon dioxide laser treatment for prominent telangectasias.

Papulopustular rosacea is usually treated with topical agents and/or systemic antibiotics.

Phymatous rosacea is uncommon. Effective therapies include surgery and laser therapy.

Ocular rosacea is managed with eyelid hygiene, artificial tears, and topical metronidazole. Persistent or severe symptoms should prompt referral to an ophthalmologist.

Patient can access accurate information on websites such as the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org).

Treatment of the older patient is similar to that of other ages. However, the possibility of impaired renal and liver function and polypharmacy in these patients needs to be considered.

Older patients may need their treatment regimes explained several times in more than one medium.

for reduced renal or liver function in the older patient, and the likelihood that these individuals may be taking multiple other medications.

No competing financial interests declared.

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