



Triggers and treatment of rosacea

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Key points

- Rosacea is a common condition characterised by flushing, erythema, inflammatory lesions and telangiectasia.
- The cause is multifactorial and not completely understood: genetics, neurovascular dysregulation and infections may be involved.
- Diagnosis of rosacea is based on clinical findings, although investigations may be required to exclude differential diagnoses.
- Treatment is tailored to the individual and aims to control symptoms and signs, but not cure the disease.
- Referral of the patient to a general dermatologist is recommended when rosacea does not respond to conventional therapy.
- Referral of the patient to an ophthalmologist is recommended if eye involvement is suspected.

Rosacea is a common chronic inflammatory skin condition that can lead to significant facial changes, ocular involvement and decreased quality of life. Its cause is multifactorial and not completely understood. Treatment aims to control, but not cure, the disease.

Rosacea is a common chronic inflammatory skin disease primarily affecting the facial convexities. It is characterised by vascular lability, leading to flushing, telangiectasia and fixed erythema, and cutaneous inflammation, manifesting as papules, pustules and lymphoedema. Although not life-threatening, rosacea may have a significant impact on a patient's self-esteem and quality of life. Early diagnosis and treatment will reduce morbidity.

EPIDEMIOLOGY

Estimated prevalence rates of rosacea range from 0.9 to 22%. The largest studies estimate prevalence at 2 to 3% of the general population.¹

Rosacea tends to occur in adults over the age of 30 years. In groups aged younger than 35 years or older than 50 years, men and women are affected equally; however, there is a predominance in women in the 36- to 50-year age group.¹ Incidence is highest in people with skin types I and II, although it does also occur in people with Asian and pigmented skin types.²

PATHOPHYSIOLOGY

The pathophysiology of rosacea is multifactorial and not completely understood. At present, rosacea is thought of as a complex inflammatory disorder arising in genetically predisposed individuals.

Genetics

Rosacea often affects multiple family members. Recent analyses have found distinct genetic profiles for each rosacea subtype, with expression of more than 500 different genes compared with healthy skin.³ The skin of patients with rosacea has been found to be dry and acidic, with altered sebum fatty acid composition.⁴

Neurovascular dysregulation and augmented immune detection and response

Precipitating and exacerbating factors associated with rosacea include alcohol intake, heat, cold, exercise, smoking, eating spicy food, drinking hot beverages and stress. Patients with rosacea have a greater immunological response to these triggers,

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resulting in cellular infiltration, increased vasculature and an influx of proteolytic enzymes into the stratum corneum.

Some of the factors implicated in causing rosacea include cathelicidin, vascular endothelial growth factor and substance P. The understanding of the innate immune response and host defence peptides, known as antimicrobial peptides (AMPs), is an exciting area of research in general medicine. The concentration of an AMP known as cathelicidin LL-37, is increased in patients with rosacea-prone skin. Such discoveries may have ramifications for future targeted therapies.^{3,5,6}

Infection

Certain infections have been implicated as causes of rosacea. The face mite *Demodex folliculorum*, an obligatory parasite of human pilosebaceous follicles, has been identified in elevated numbers in patients with rosacea. It is hypothesised that an immune defect allows the mite to penetrate the dermis and stimulate an exaggerated immune response, giving rise to the papules and pustules of rosacea.⁷ In other studies, abundant numbers of the commensal Gram-positive bacterium *Staphylococcus epidermidis* have been detected in patients with pustular rosacea. Significantly, strains were the beta-haemolytic variant, differing from the nonhaemolytic form isolated from normal controls.^{8,9} Although *Helicobacter pylori* has also been implicated in the development of rosacea, studies have yielded contradictory results.¹⁰

CLINICAL FEATURES

The clinical presentation of patients with rosacea is variable. Areas of the body typically affected are the central convex areas of the face (cheeks, nose, chin and forehead). Occasionally the scalp, upper chest, back and even limbs may be involved.¹¹

Diagnosis of rosacea is based on the presence of the clinical features listed below.¹²

- Presence of one or more of the following primary features:



Figure 1. Erythematotelangiectatic rosacea.

- flushing (transient or reversible erythema): a history of frequent blushing or flushing spontaneously or in response to various stimuli is common
- erythema (fixed or persistent) of the facial skin: this is common
- inflammatory lesions: these typically appear as dome-shaped red papules with or without pustules; comedones are absent
- telangiectasia: these are usually linear, dilated capillaries of varying diameter, fine, medium or coarse.
- Possible presence of one or more of the following secondary features:
 - burning or stinging sensations
 - erythematous plaques
 - rough or scaly central facial skin
 - oedema accompanying or following facial erythema
 - ocular manifestations, including burning sensation, dry gritty eyes, conjunctival hyperaemia
 - involvement of peripheral locations, e.g. limbs
 - phymatous changes due to sebaceous tissue hypertrophy: the most common form, rhinophyma, affects the nasal skin.

Subtypes of rosacea

There are four primary subtypes of rosacea. One subtype may progress to another or they can occur in isolation.



Figure 2. Papulopustular rosacea.

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is characterised by flushing and persistent central facial erythema (Figure 1). Telangiectases may be present, and patients may report central facial oedema, stinging, burning, roughness or scaling.¹²

Papulopustular rosacea

Papulopustular rosacea is characterised by persistent central facial erythema with transient papules and/or pustules in the central facial distribution (Figure 2). Comedones are absent, in contrast to acne, and burning and stinging may be present. This subtype of rosacea is often seen in combination with or develops after erythematotelangiectatic rosacea.¹²

Phymatous rosacea

Phymatous rosacea refers to hypertrophy of sebaceous glands and fibrous thickening of the skin due to chronic inflammation (Figure 3). It clinically manifests as tissue enlargement, prominent pores and nodularity of the skin surface.

The most common presentation is rhinophyma, characterised by coarse thick



Figure 3. Phymatous rosacea – demonstrating rhinophyma.

nasal skin particularly involving the nasal tip; it is commonly referred to as ‘alcoholic’ or ‘potato’ nose. Interestingly, other locations may be involved, including the ears (otophyma), forehead (metophyma), eyelids (blepharophyma) and chin (gnatophyma). This subtype is often seen in combination with, or develops after, erythematotelangiectatic or papulopustular rosacea subtypes.¹²

Ocular rosacea

Ocular rosacea occurs in up to 70% of patients with rosacea. One-third of these patients may develop corneal involvement, which is potentially sight-threatening.^{13,14} Further details are given below in the section ‘Associations and complications’ on page 39.

DIFFERENTIAL DIAGNOSES

Seborrhoeic dermatitis

Seborrhoeic dermatitis may coexist with rosacea. It is best differentiated by the presence of greasy scale in the nasolabial folds, external ear canals and central eyebrow region.²

Acne vulgaris

Acne vulgaris tends to occur in a younger age group and is characterised by the presence of open and closed comedones. It can also coexist with rosacea.²

Steroid-induced acneiform eruption

Steroid-induced acneiform eruption is an inflammatory response that can occur during or after chronic topical and systemic corticosteroid use.¹²

Perioral dermatitis

Perioral dermatitis is characterised by erythema, microvesicles and scaling around the mouth, nose or eyes.¹² It is commonly induced by topical corticosteroids or occlusive skincare products such as emollients, sunscreens and cosmetics.

Lupus erythematosus

The presence of pustules, papules or blepharitis favours a diagnosis of rosacea, whereas scaling, follicular plugging, pigmentary disturbance and scarring favour discoid lupus erythematosus (DLE) as the diagnosis. Histological examination may be necessary to make a distinction between the two. Both eruptions can be photo-aggravated. Systemic lupus erythematosus (SLE) and subacute cutaneous lupus erythematosus (SCLE) are less common.²

Cutaneous sarcoidosis of the nose (lupus pernio)

This condition may resemble rhinophymatous rosacea; however, there is minimal skin surface change in patients with cutaneous sarcoidosis of the nose.¹¹

Tinea faciei

Tinea faciei is an infection of the facial skin by dermatophyte fungi. Diagnosis is confirmed by microscopy and culture of skin scrapings.

Essential telangiectasia

Patients with essential telangiectasia will only have this condition and no other features of rosacea.

Carcinoid syndrome

In patients who present with severe or sudden-onset facial flushing, it is worth investigating for carcinoid syndrome. Gastrointestinal, cardiac and pulmonary

DIFFERENTIAL DIAGNOSES OF ROSACEA

- Acne vulgaris
- Seborrhoeic dermatitis
- Perioral dermatitis
- Steroid-induced acneiform eruption (steroid rosacea)
- Lupus erythematosus – discoid, systemic or subacute cutaneous
- Cutaneous sarcoidosis of the nose (lupus pernio)
- Tinea faciei
- Essential telangiectasia
- Carcinoid syndrome
- Drug reaction
- Polymorphous light eruption
- Atypical infections
- Contact dermatitis – irritant or allergic
- Lupus vulgaris (cutaneous tuberculosis)
- Acne agminata
- Dermatomyositis
- Polycythaemia rubra vera
- Superior vena cava obstruction

symptoms may be present.

A list of differential diagnoses is provided in the box.

INVESTIGATIONS

Minimal investigations are required as the diagnosis of rosacea is usually based on history and clinical findings. Baseline blood test results including full blood count and kidney and liver function tests are necessary if the use of systemic therapy is being considered. A skin scraping is useful to exclude fungal infection. Autoimmune serology (antinuclear antibodies [ANA] and extractable nuclear antigens [ENA]) should be performed if a connective tissue disease such as lupus is suspected. Creatine kinase (CK) levels should be checked for dermatomyositis. Skin biopsy (for haematoxylin and eosin staining, immunofluorescence

with or without culture) is worthwhile if symptoms are atypical, the diagnosis remains unclear or the condition is unresponsive to conventional therapy.¹⁵

Histological findings

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is characterised by the presence of enlarged dilated capillaries and venules in the upper dermis. These vessels may be unusually shaped (e.g. tortuous or geometric). *Demodex* mites are commonly present in affected patients. Other features include oedema in the upper dermis, lymphocytic inflammation and spongiosis.

The dermoepidermal junction appears normal in patients with rosacea, unlike in those with lupus erythematosus in which there are lichenoid changes at this junction.¹⁵

Papulopustular rosacea

Papulopustular rosacea is characterised by a mixed inflammatory cell infiltrate, with numerous plasma cells, neutrophils and sometimes eosinophils. *Demodex* mites are often present in affected patients, as are spongiosis and solar elastosis. Retentional elements, such as comedones and dermal infundibular cysts, are absent, helping to differentiate papulopustular rosacea from papulopustular acne.¹⁵

Phymatous rosacea

Phymatous rosacea commonly presents with rhinophyma, which is characterised by an increased volume of sebaceous glands and fibrosis. The sebaceous lobules are of normal structure but extremely large. The infundibula are also enlarged and filled with keratin, eosinophilic debris and organisms, commonly *Demodex* mites.¹⁵

MANAGEMENT

Education

It is important from the outset to explain to patients that rosacea is a chronic skin condition that can be controlled but not cured. Reassure them that it is generally responsive to treatment and rarely scars

TABLE. THERAPIES DIRECTED AT THE ROSACEA SUBTYPE

Subtype of rosacea	Therapies
Erythematotelangiectatic	Topical brimonidine Vascular laser and intense pulsed light
Papulopustular	Topical metronidazole Topical azelaic acid Oral doxycycline or minocycline Isotretinoin
Phymatous	Isotretinoin Ablative laser Surgery

the skin. Improvement may be gradual, so patients need to persevere with treatment. Therapy should be trialled for at least three months to assess efficacy, and may be needed intermittently or continuously for years.¹¹

Of course, if the patient is asymptomatic, no treatment is an option.

Avoid precipitants

In patients with mild rosacea, avoidance of triggers may be enough to improve the condition. Triggers to consider avoiding include extremes of temperature (hot or cold), ultraviolet (UV) radiation exposure, intake of spicy foods, hot or alcoholic beverages, wind, exercise and stress.^{2,11}

Affected patients should avoid using topical corticosteroid agents. Although immediate improvement may be observed after application of a corticosteroid due to their vasoconstrictive and anti-inflammatory effects, in the long term topical corticosteroids worsen rosacea and may trigger acneiform eruptions.

Encourage patients to apply a cool, damp (tap water) soft cotton compress regularly to the facial skin for 10 minutes to reduce symptoms such as burning and stinging.

General skin care measures

Patients with rosacea should minimise their use of skin care products and cosmetics ('less is more'). Fragrance- and preservative-free cleansers and light emollient

creams are usually all that are needed. Patients should use their fingers to apply the products (not foam pads or brushes) to minimise mechanical disruption of the skin barrier. Application of potential irritants, such as soap bars, toners and alcohol-based cleansers, should be avoided, as should products containing menthol, camphor and sodium lauryl sulphate.¹⁶

As sunlight is a common trigger for rosacea flare-ups, patients should wear a broad-spectrum low irritant SPF 50+ sunscreen daily, and limit sun exposure by wearing protective clothing and hats. Shade should be sought when outdoors, and patients should be encouraged to stay indoors during periods of high UV radiation. Sunscreens containing the physical blockers titanium dioxide and zinc oxide are well tolerated by most patients, and newer chemical agents are proving to be less irritant.¹⁶

Makeup may be used to conceal the signs of rosacea. Waterproof cosmetics and heavy foundations should be avoided, because these are difficult to remove without the use of irritating solvents and abrasive cloths. Green-tinted concealer helps camouflage erythema.¹⁶

Topical therapies

Fortunately a wide range of topical agents are effective as first-line therapy for patients with rosacea and a limited number of papules and pustules. Careful consideration must be given to the vehicle used to deliver



Figures 4a and b. Telangiectases. Before (a, left) and after (b, right) treatment with pulsed dye laser.

the active agent because this will affect tolerability (in view of altered skin barrier function), patient compliance and efficacy.¹⁷ Formulations available include gels, lotions, creams, foams and ointments.

Metronidazole

Topical metronidazole 0.5 to 0.75% (available as a cream or gel) applied once or twice daily is effective in treating patients with papulopustular rosacea and has been used since the 1980s. It may also reduce blanchable erythema (but not telangiectasia) in patients with erythematotelangiectatic rosacea. Anecdotally, patients with sensitive skin tolerate the cream formulation best, whereas men tend to prefer the gel base. Several weeks of application are required to see obvious improvement and it may be used on a long-term basis to maintain remission.

Patients should be advised that topical agents work best when applied to an entire affected area rather than as spot treatment.^{2,14,16}

Alpha-adrenoreceptor agonists

Topical brimonidine 0.33% gel is a promising new therapy approved in Australia in 2014 for intermittent topical treatment of patients with the persistent facial erythema of rosacea. It targets the alpha-adrenoreceptors in the smooth muscle of superficial cutaneous blood vessel walls. Application reduces erythema within 30 minutes, with the peak effect lasting three to six hours, and gradual return to

baseline 12 hours after application. Phase 3 trials showed no major adverse reactions besides occasional mild and transient skin irritation. Specifically, no significant tachyphylaxis or rebound erythema was noted.⁵

Azelaic acid

Topical azelaic acid (available as a 20% lotion or 15% gel) applied once or twice daily is an alternative to topical metronidazole in the treatment of patients with papulopustular rosacea. Although studies show it to be more efficacious than metronidazole, it can be more irritating, so patients should be advised to apply the preparation every second or third day initially.¹⁴

Other topical agents

Other topical agents such as compounded tacrolimus 0.03%, pimecrolimus 1%, compounded sodium sulfacetamide 10% with sulphur 5%, and clindamycin 1% (off-label use) may be useful in certain cases of rosacea.¹⁶

Oral therapies

Oral therapy is preferable when the skin lesions of rosacea are more extensive or when patients have not responded to topical therapy. Topical therapy may be added to the treatment regimen once the inflammation has begun to settle with the systemic agent; this minimises potential irritation. Once the rosacea improves, the systemic therapy may be discontinued and improvement maintained with topical treatment alone.^{2,14}

Tetracyclines

Oral tetracyclines have anti-inflammatory properties and have been the mainstay of treatment for patients with rosacea for decades. They are particularly effective in treating patients with papulopustular rosacea.

With the loss of tetracycline hydrochloride from the Australian market, doxycycline (off-label use) has become the drug of choice. Doses of 50 to 100 mg/day



Figure 5. Erythema and spot purpura immediately after pulsed dye laser therapy.

have been used traditionally but recent studies show subantimicrobial doses of 40 mg/day are as effective (see novel therapies below).¹⁸ Minocycline (off-label use; 50 to 100 mg/day) is also used to treat patients with papulopustular rosacea and is more lipophilic.

Chronic use of oral tetracyclines has been associated with the development of irreversible blue-grey pigmentation and drug-induced systemic lupus in a small percentage of patients. Response can be seen within four weeks. Intermittent use is preferable.

Metronidazole

Oral metronidazole (off-label use) 200 mg twice daily may be trialled in patients with rosacea in whom tetracyclines are contraindicated or ineffective. However, patients must abstain from alcohol intake during metronidazole therapy to avoid alcohol-induced headaches via disulfiram reactions.¹⁶

Other antibiotics

Studies have shown oral clarithromycin and azithromycin to be useful in the treatment of patients with rosacea (off-label uses).¹⁶ Trimethoprim-sulfamethoxazole and ciprofloxacin are not generally used due to concerns of resistant bacterial populations. Penicillins and cephalosporins

are generally ineffective in the treatment of patients with rosacea.²

Isotretinoin

Low-dose isotretinoin (off-label use) may be effective in patients with severe papulopustular or phymatous rosacea. Referral of these patients to a dermatologist is advised. Patients with refractory disease typically respond well to doses of 10 to 20 mg/day; long-term maintenance therapy may be required as the lasting response seen in acne does not often occur in rosacea.²

Other oral therapies

Other oral therapies reported to be effective in patients with rosacea include clonidine, spironolactone, naloxone and ondansetron (all off-label use).¹⁶ Single-dose oral ivermectin (off-label use) has been used in immunocompromised patients with rosacea-like demodicidosis with good effect.¹⁸

NSAIDs, such as diclofenac, may offer symptomatic relief in patients with rosacea.

Physical therapies

Laser and light

Vascular laser therapy, such as with the 595 nm pulsed dye laser, and intense pulsed light therapy can be used to remove refractory background erythema and clinically significant telangiectases (Figures 4a and b). The light in these devices is absorbed by oxyhaemoglobin and haemoglobin, leading to vessel destruction with minimal collateral tissue damage (Figure 5).¹⁶ Ablative lasers can be used for the contouring of hypertrophied tissue in patients with phymatous rosacea.^{2,14} Patients may be referred to a dermatologist for laser therapy.

Rhinophyma can be debulked by an ablative resurfacing laser (e.g. carbon dioxide) or radiofrequency electrosurgery devices. Treatment is aimed at debulking the excess tissue and then sculpting the disfigured nose. These devices are preferred for recontouring because there is

little blood loss compared with scalpel excision.

Surgery

Scalpel excision has been used to debulk and sculpt the nose but is less precise than laser therapy.

Novel therapies

Subantimicrobial-dose tetracyclines

At higher doses the oral tetracyclines are antimicrobial; at lower doses they have anti-inflammatory actions without antibiotic activity. Doxycycline 40 mg once daily (delayed release) or 20 mg twice daily is effective in the treatment of patients with rosacea, without any development of antibiotic resistance or impact on skin flora. Efficacy is comparable with traditional dosing of doxycycline but there are fewer adverse effects.¹⁸ A slow-release doxycycline preparation is not currently available in Australia.

Beta-blockers

Nonselective beta-blockers decrease sympathetic activity and produce vasoconstriction, which suppresses flushing. Oral propranolol 30 to 120 mg/day and carvedilol 15 to 25 mg/day have been shown to reduce the frequency and severity of flushing episodes (both off-label use). They may be used in normotensive patients as long as doses are gradually escalated and blood pressure monitored.¹⁸

Other antimicrobials

Topical 5% permethrin, 10% crotamiton and 1% ivermectin (all off-label use) have been reported to be useful in patients with rosacea. However, they should be used with caution as they may irritate sensitive skin.¹⁸

PROGNOSIS

The duration of rosacea is highly variable, ranging from months to decades. Treatment of affected patients aims to suppress symptoms and prevent disease progression and complications; it does not appear to alter disease duration.

The course of rosacea fluctuates, characteristically waxing and waning in response to the various stimuli discussed above. When persistent, rosacea results in fixed facial erythema. Only a portion of patients, usually men, develop cutaneous hypertrophy, and this manifests most commonly as rhinophyma.¹¹

ASSOCIATIONS AND COMPLICATIONS

Psychosocial impact

Although rosacea is not a life-threatening disease, the impact on a patient's quality of life can be significant. Rosacea may cause embarrassment, anxiety, decreased self-esteem and social isolation. Patients may feel self-conscious of their 'alcoholic nose' or report disappointment that their disease cannot be cured.¹⁹ These feelings should be taken into account when devising a treatment plan. Online support groups such as the Rosacea Support Group (<http://rosacea-support.org/australia>) can be useful.

Ocular rosacea

At least 70% of patients with rosacea experience ocular symptoms, with men and women being affected equally. Symptoms are often mild, so it is worth specifically asking about ocular involvement at the first consultation. Severe eye involvement may lead to ocular keratitis with subsequent scarring, corneal perforation and vision loss.¹³

Symptoms include tearing, conjunctival hyperaemia, foreign body sensation, burning, stinging, dryness, itching, light sensitivity and blurred vision. When the cornea is involved, patients may report decreased visual acuity. Other signs include telangiectases of the conjunctiva and lid margin, lid and periocular erythema, blepharitis, conjunctivitis and styes.¹³

Early consultation with an ophthalmologist is recommended as slit lamp examination of the ocular surface is needed.^{13,14} It is worth noting that ocular rosacea may occur in the absence of cutaneous manifestations, and the severity of ocular symptoms is not necessarily related to the severity of cutaneous findings.¹³

General measures to relieve ocular symptoms include application of warm compresses and lubricating eye drops. Mild rosacea can be treated with topical cyclosporin 0.05% (off-label use), which increases tear production and has mild anti-inflammatory effects, and antibiotic ointments to decrease eye flora. Metronidazole gel is useful in cases of rosacea-associated blepharitis. Topical corticosteroids may be used to settle inflammation; however, long-term use should be avoided because of increased risk of ocular infections and potential side effects such as glaucoma and cataracts. Moderate to severe ocular rosacea may require systemic therapies such as oral doxycycline or, as second-line, azithromycin.^{13,14} Regular lubrication of eyes is essential when using oral isotretinoin for cutaneous rosacea.

Lymphoedema

Chronic inflammation in patients with long-standing rosacea damages local lymphatic vessels, resulting in a build-up of protein-rich lymphatic fluid in the skin (lymphoedema). Although an uncommon complication of rosacea, lymphoedema preferentially affects periorbital skin, resulting in eyelid swelling and even ectropion.¹¹ It can be acute or subacute in onset, and unilateral or bilateral in distribution.

Salivary gland involvement

Although rare, inflammation of the salivary glands as a consequence of rosacea can result in reduced salivary secretions and dry mouth.¹¹

CONCLUSION

Rosacea is a common chronic inflammatory skin disease that often impacts significantly on the patient's quality of life. Referral to a dermatologist is recommended when the disease is not responding to conventional therapy or for consideration of laser or light therapies. Ophthalmology review is recommended if eye involvement is suspected. General measures such as avoidance of known precipitants and use of fragrance- and preservative-free skin care products are paramount to the

management of the condition.

With the renewed interest in the pathogenesis of rosacea, particularly at both the microbiota²⁰ and immunological⁶ levels, novel topical and systemic agents are under development. An exciting area of translational research is the inactivation of enzymes of the kallikrein family, which should reduce cathelicidin levels in patients with rosacea-prone skin and thus prevent aberrant activation of the innate immune response.²¹

MI

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