Rosacea: causes and treatments

Rosacea can cause sufferers considerable distress and embarrassment. Recent advances in our understanding of the factors involved in this condition could point the way to more effective treatments

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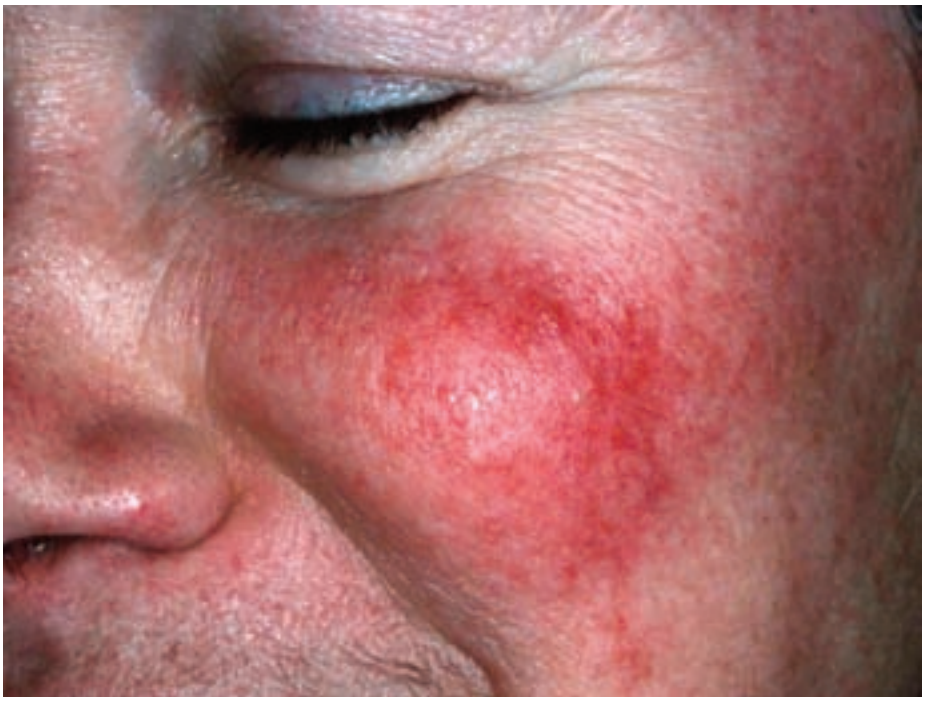
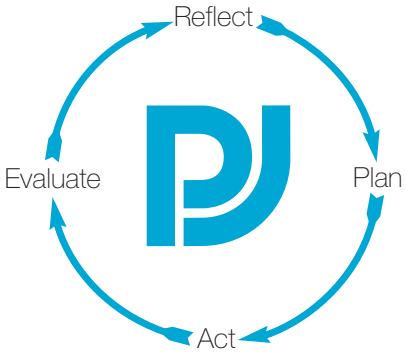




REFLECT

1 What medicines might worsen rosacea?
2 What is the rationale behind the use of antibiotics to treat rosacea?
3 Would you be able to discuss therapy options with a patient with rosacea?

Before reading on, think about how this article may help you to do your job better.

In the past rosacea was often called "acne rosacea" or "red acne" but dermatologists now believe that acne and rosacea are separate conditions.

Rosacea is a chronic condition characterised by recurrent episodes of facial flushing, persistent erythema, telangiectasia (visibly dilated blood vessels at the skin surface), and papules and pustules. Many people with rosacea also have symptoms in and around the eyes, such as blurred vision and blepharitis. A small number of patients experience hypertrophy of the sebaceous glands of the nose, resulting in the nose becoming enlarged (rhinophyma) and reddened.

Rosacea usually presents in people who are fair-skinned, and between the ages of 30 and 50 years. It is more common in women, but tends to be more severe in men.[1]

Although rosacea is always described as common, accurate estimates of prevalence are lacking. This is probably, in part, due to the difficulties of distinguishing rosacea from other conditions, such as chronic sun damage. However, in two European studies the prevalence of rosacea was reported to be 1.5 per cent and 10 per cent.[1]

Eye problems are experienced by about 50 per cent of people with rosacea.

Diagnosis and subtypes

Rosacea describes a collection of changes in the facial skin and eyes. In recent years, a symptom-based system has been developed to classify the condition into four subtypes:

1) Erythematotelangiectatic rosacea (ETR)
2) Papulopustular rosacea (PPR)
3) Phymatous rosacea
4) Ocular rosacea

Panel 1 (p2) describes these subtypes. A more detailed version of this classification system includes criteria to grade cases (see Resources).

No formal test or laboratory measurement can confirm the diagnosis but diagnostic guidelines exist (see Panel 2, p2).[2]

It is important to differentiate PPR from acne vulgaris, peri-oral dermatitis and seborrhoeic dermatitis to ensure the correct treatment.

It should be noted that flushing is often, but not always, not always a feature of rosacea. Patients who have prolonged episodes of severe flushing that are not limited to the face and are accompanied by systemic symptoms should be referred because rare conditions, such as phaeochromocytoma or carcinoid syndrome, can give rise to this presentation.

Causes

The causes and pathogenesis of rosacea are not yet fully understood. However, improved understanding of the immune and inflammatory mechanisms in the skin and recent research in the field are leading to plausible hypotheses that could lead to more effective treatments.

Suggested causes have included diet, alcohol, psychosomatic illness, visual display units and *Helicobacter pylori*. Spicy food, alcohol and hot drinks can trigger flushing in rosacea patients but there is no evidence that these agents have a primary role in the development of the condition. →

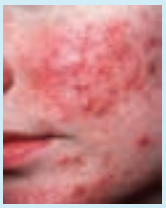
KEY POINTS

- Rosacea is a remitting and relapsing condition affecting the face, which can be distressing for sufferers.
- Rosacea can also cause eye problems.
- There is no cure for rosacea. Treatments include antibiotics, retinoids and acaricides.
- A large part of management is to avoid activities that can cause facial flushing.

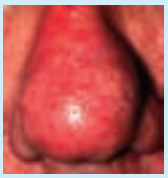
PANEL 1: SUBTYPES*

Erythematotelangiectatic rosacea (ETR; subtype1) Features include flushing and persistent central facial erythema with or without telangiectasia. ETR is usually seen in people with sensitive skin and who are poorly tolerant of topical treatments.

Papulopustular rosacea (PPR; subtype 2) PPR features persistent central facial erythema with transient central facial papules or pustules, or both. In severe cases lesions coalesce to form plaques. There can also be telangiectasia, oedema and flushing.



Phymatous rosacea (subtype 3) Features are thickening skin, irregular surface nodularities and enlargement of tissue. The nose, chin forehead, cheeks or ears can be affected.



Ocular rosacea (subtype 4) Sufferers can experience burning, stinging, dryness and itching in or around the eyes, blepharitis, photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, and peri-orbital oedema. Symptoms also include the sensation of a foreign body in the eye.

*Adapted from Standard classification of rosacea. 2002.

PANEL 2: GUIDELINES FOR DIAGNOSIS[2]

Diagnosis requires the presence of one or more of the following primary features affecting the facial skin:

- Flushing (transient erythema)
- Non-transient erythema
- Papules and pustules
- Telangiectasia

The condition can include one or more of the following secondary features:

- Burning or stinging skin
- Plaque(s)
- Dry or rough skin
- Oedema (facial swelling)
- Eye problems
- Peripheral location (eg, neck, chest, scalp)
- Phymatous changes

The notion that *H pylori* might play a causative role in rosacea gained currency in the 1990s. It has been suggested that it might stimulate the production of bradykinin, which has vasodilatory action. The organism is widely distributed in the general population and, unsurprisingly, it is commonly found in patients with rosacea. Treatments aimed at eradicating *H pylori* can temporarily improve rosacea but, at present, convincing evidence for a causative role for this organism is lacking. One study in 2009 showed no differences between patients (n=172) and controls (n=145) for *H pylori* serostatus, caffeine intake, alcohol consumption, occupational environment or education level.[3]

Risk factors for rosacea include photosensitive skin types, family history of rosacea and previous smoking status. The use of drugs, such as corticosteroids or hormones, might also present a risk.

There is a highly significant association between ETR and sun damage, and it has even been suggested that ETR is a photosensitive disease. PPR, in contrast, is not associated with sun damage.

Disorder of the immune system

People with rosacea are more sensitive to stimuli that do not cause inflammatory reactions in those without rosacea. Recent attention has turned to cutaneous vascular abnormalities, climatic exposure and abnormalities of the pilosebaceous unit (the hair shaft and follicle and the sebaceous gland). All of these are linked by a unifying hypothesis, which proposes that rosacea is the result of impaired regulation of the innate immune system.

The innate immune system of the skin is normally programmed to detect microbes and tissue damage, such as UV-induced apoptosis or damage to the extracellular matrix — known triggers of rosacea. The innate immune response is also triggered by stimuli previously associated with worsening of the disease (eg, sun exposure).

Cathelicidin The innate immune system in the skin comprises cells and mechanisms that provide a rapid, short-lasting, non-specific response to environmental stimuli. Once activated, cytokines and antimicrobial molecules are released, including a peptide known as cathelicidin. Some forms of cathelicidin have both vasoactive and pro-inflammatory properties, suggesting a key role for this peptide in rosacea.

Researchers have also discovered that people with rosacea express abnormally high levels of cathelicidin. Furthermore, the forms found in rosacea are different from those in controls. These forms of cathelicidin promote and regulate leukocyte chemotaxis, angiogenesis, and the expression of extracellular matrix components.

The hypothesis was confirmed when injection of abnormal cathelicidin into mice produced the characteristic inflammatory changes of rosacea. The researchers postulated that an exaggerated innate immune response induces abnormal cathelicidin and this leads to the characteristic clinical picture of rosacea.[4]

Toll-like receptors Another piece in the jigsaw is toll-like receptors (TLRs) — non-specific receptors that are involved in detecting immune stimuli. Studies have shown that TLR2 expression is altered in rosacea-affected skin, which enhances skin susceptiblity to innate immune stimuli and leads to increased kallikrein and cathelicidin production.

Demodex mites

A 0.3mm long parasitic mite, *Demodex folliculorum*, could be one of the triggers of the the innate immune response. *D folliculorum* is a normal resident of skin that feeds on sebum and keratinocytes. In normal facial skin the demodex density (Dd) is up to 5 per cm^2, the population normally held in check by a combination of humoral and cell-mediated immunity.[5] The mites can penetrate the epithelium but in healthy skin their presence is asymptomatic.

Large numbers of demodex mites on the skin is described as demodicosis. When unusually large numbers of the mites are present they can be seen as a fine white scale at the base of each hair follicle on the face. This creates a frosted appearance known as pityriasis folliculorum, which can be so severe as to give a false sensation of dry skin.[5] Typical Dd counts in patients with pityriasis folliculorum range from 61 to 308 mites per cm^2. Pityriasis folliculorum is typically seen in older women who do not use soap and apply large amounts of makeup.

There is no animal model for demodex infestation because the mite is an obligate human parasite. It is assumed to have a pathogenic role when a skin disease with a high Dd is cured by acaricidal treatment and the Dd simultaneously falls to normal.

Demodex mites have been linked to a number of features of rosacea, including papules and pustules, folliculitis and blepharitis. In addition, significantly higher Dds are found in patients with rosacea than in age-matched controls.

Sun-damaged skin is thought to favour the proliferation of mites on the skin by two mechanisms, first by causing ETR (and thereby providing a hypervascularised base) and, secondly, by immunosuppressive action on local cell-mediated immunity, enabling the mites to multiply more easily.

PPR is associated with a type IV immunological reaction (expressed as papulopustules) induced by the mites, believed to be a means of defence against mite

Christine Clark will be available to answer questions online on the topic of this article until 6 June 2011

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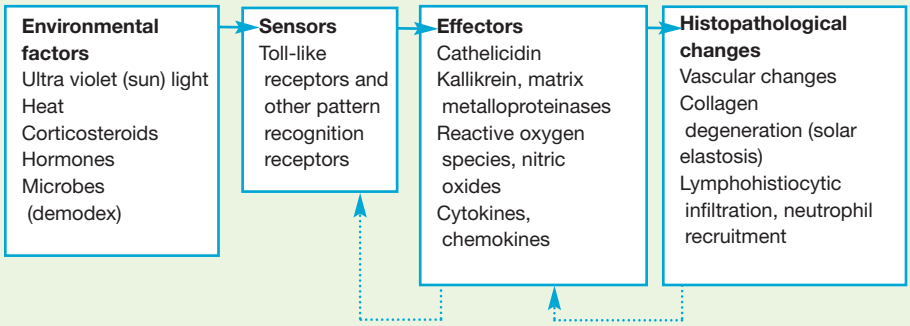

Adapted from Journal of Dermatological Science, 55. Yamasaki *et al*), The molecular pathology of rosacea, Pages 77–81. Copyright (2009), with permission from Elsevier.

Figure 1: Suggested molecular mechanisms in rosacea

proliferation.[5] Patients with PPR have a higher Dd than controls but lower than those with pityriasis folliculorum. PPR appears to be due to an exaggerated immune reaction. The recent finding of *Bacillus oleronius* in Demodex mites raises the possibility that the triggering antigen could be bacterial in origin.

Suggested molecular mechanisms for rosacea are summarised in Figure 1.

Prognosis, effects and complications

Rosacea is a relapsing and remitting condition. The main problem is that there is no cure and for many sufferers facial appearance and behaviour of their skin is a source of considerable embarrassment and distress. This is often exacerbated by the popular perception that a flushed face and red nose are caused by over-indulgence in alcohol. The psychological impact of rosacea should not be underestimated.

Ocular rosacea can cause serious problems and some patients can even experience loss of vision as a result of corneal complications such as punctate keratitis, corneal infiltrates ulcers or marginal keratitis.[2]

Rhinophyma is a rare but distressing complication. It is almost always confined to men over 40 years of age. More rarely, similar changes may develop in the chin, forehead, cheeks or ears.

Management

Uncertainty about the causes and pathogenesis of rosacea has prompted the use of a wide range of treatments. The limited effectiveness of many of the products prescribed has also meant that lifestyle advice (eg, to avoid activities that cause facial flushing — see below) is a large part of management.

Treating ETR

Good skin care and non-pharmacological measures (see below) are key in managing ETR because patients' skin tends to be sensitive and easily irritated. In addition, although the topical and systemic treatments recommended for PPR are also often prescribed for ETR, there is little evidence for their efficacy in this subtype. Laser ablation of telangiectatic vessels can be undertaken if necessary.

Treating PPR

Topical treatments can be adequate for mild PPR whereas moderate-severe disease usually requires systemic treatment. Treatment should be continued for 12 weeks[6] because the onset of action can often be gradual. However, relapse is common after treatment is discontinued so some dermatologists recommend continued treatment for six months.

Antimicrobials Systemic or topical antimicrobial treatments recommended by the BNF and Clinical Knowledge Summaries include topical metronidazole or azelaic acid (Finacea) for mild to moderate PPR and oral tetracyclines or erythromycin for moderate to severe PPR.

It is thought that the mechanisms of action of these antimicrobials are anti-inflammatory rather than antibacterial. Indeed, tetracyclines are effective in rosacea at doses below those required for treatment of bacterial infections. One product (Efracea) contains a low dose of doxycycline (40mg) for this reason. Doses of other oral antibiotics are the same as those used in acne and six to 12 week courses are repeated intermittently.

The summary of product characteristics for Efracea states: "The pathophysiology of the inflammatory lesions of rosacea is, in part, a manifestation of a neutrophil-mediated process. Doxycycline has been shown to inhibit neutrophil activity and several pro-inflammatory reactions, including those associated with phospholipase A2, endogenous nitric oxide and interleukin-6." However, it adds that the clinical significance of these findings is not known. It also states that the plasma concentration of doxycycline following administration of Efracea is "well below the level required to inhibit micro-organisms commonly associated with bacterial diseases".

The main problems with treatment with antibiotics are the risk of emergence of resistance in normal microflora and rapid relapse after treatment is discontinued. So, for example, the SPC for Efracea recommends that patients should be assessed four weeks after stopping treatment.

The SPC for Finacea states: "The mechanism by which azelaic acid interferes with the pathogenic events in rosacea is unknown. Several *in vitro* and *ex vivo* investigations indicate that azelaic acid may exert an anti-inflammatory effect by reducing the formation of pro-inflammatory, reactive oxygen species."

Finacea gel should be applied sparingly to the affected areas — 2.5 cm of gel should be enough to cover the face. It should be applied and massaged gently into cleaned and dried skin, morning and evening. Care should be taken to avoid contact with the eyes, mouth and other mucous membranes.

According to CKS, azelaic acid may be more effective than topical metronidazole, but is less well tolerated and can cause transient stinging. If irritation occurs patients can be advised to reduce the amount of gel per application or the frequency of use to once daily (rather than twice daily) until it ceases. Although the gel should be used continuously, treatment can also be interrupted for a few days if necessary. Interrupting or reducing treatment can also be advised to those experiencing irritation with metronidazole gel. CKS says that metronidazole cream might be more suitable than the gel for sensitive skin.

Those prescribed topical metronidazole should be advised to avoid strong sunlight during use. Pharmacists might like to point out to patients that they will need to continue using their medicines for several months and to ask their GP for further supplies.

Retinoids Dermatologists occasionally recommend the use of topical or low dose oral isotretinoin although this is an unlicensed indication and the drug's drying effects on eyes and mucous membranes can be poorly tolerated. It is thought that oral retinoids work by reducing sebum secretion, making the environment less welcoming for demodex mites. The main drawback is rapid relapse after treatment is stopped.

Acaricides Treatment with an acaricide to combat demodex mites is as effective as topical metronidazole.[7] A combination of crotamiton 10 per cent and benzyl benzoate 12 per cent has been reported to be effective by a Brussels based dermatologist, Fabienne Forton (*PJ*, 7 May 2011, p526). This is prepared by a local pharmacy. Dr Forton recommends washing the face and neck twice a day with a "gentle wash product" (eg, Surgras), using a moisturiser in the morning and the acaricidal treatment in the evening. The treatment is applied to the whole

of the face, excluding the eyelids and the area close to the lips. (The benzyl benzoate is best applied to dry skin because it can sting if the skin is wet, she says).

Dr Forton also recommends the use of follow-on maintenance treatment, where the face is treated once or twice a week with the acaricidal mixture and a sulphur-based shampoo is used to cleanse the scalp once or twice a month.

For atopic patients Dr Forton uses 4 per cent benzyl benzoate or permethrin (strength as for scabies). Another option is oral ivermectin. All of these are off-label uses for the products concerned. Metronidazole, tetracyclines and topical retinoids do not reduce demodex mite population.

Other treatments Other treatments that have been used for PPR include a topical sulfacetamide product (not available in the UK), a sea buckthorn-based product and intense pulsed light. There are also anecdotal reports of the use of cucumber in yoghurt.[1]

Treating phymatous rosacea

The treatment of rhinophyma or other enlarged areas is primarily surgical and beyond the scope of this article. Patients should be advised to seek referral to a dermatologist.

Treating ocular rosacea

Treatment of ocular rosacea is important for comfort and normal functioning but also for preventing eye damage. Scrupulous eyelid hygiene is recommended (cleaning the lids with warm water twice a day), together with the use of artificial tears and metronidazole gel or fusidic acid cream applied to the lid margins. Note that the manufacturers advise that metronidazole gel can cause eyes to water.

An alternative approach is to use acaricidal treatment. The blepharitis of rosacea is linked to heavy demodex infestation and is associated with cylindrical dandruff around the eyelashes.

Lacey *et al* (see Resources) report that the dermodex mite is resistant to a number of common antiseptic solutions, including 75 per cent alcohol and 10 per cent povidone–iodine, but is killed by tea tree oil. They report that a "lid scrub" with tea tree oil removes the cylindrical dandruff and stimulates embedded mites in follicles to migrate out, and recommend a weekly lid scrub with 50 per cent tea tree oil and daily lid scrub with tea tree shampoo to eradicate ocular demodex infestation over four weeks.

Oral tetracyclines are often prescribed for moderate to severe ocular rosacea.[1] Patients with severe or troublesome ocular rosacea should be referred to an ophthalmologist.

Advice pharmacists can give

Pharmacists can reassure patients about benign nature of rosacea and the rarity of rhinophyma (especially in women). In addition, they can:

- Advise patients to avoid potentially exacerbating factors (see Panel 4).

Significantly higher *Demodex follicorum* densities are found in people with rosacea than in controls (Syred/SPL)

- Advise patients to keep a diary to identify exacerbating factors.
- Suggest a daily application of combined UVA+UVB sunscreen — SPF 15 or more. (Sunscreen can be incorporated into a regular moisturiser. Vehicle formulations with dimethicone or cyclomethicone, usually labelled "oil-free", can be less irritating than others. Sun-blocking creams containing titanium dioxide and zinc oxide are generally well tolerated.)
- Suggest daily use of mild or soap-free cleansers (eg, Dove, Cetaphil) and liquid film-forming moisturisers to improve the condition of the skin.
- Suggest cosmetic coverage of excess redness with suitable cosmetics containing inert green pigment to neutralise red appearance.
- Signpost patients to patient support groups.

Signposting

- The National Rosacea Society is a US based organisation but its website (www.rosacea.org) contains some good patient information, including on laser therapy and tips on skin care.
- Changing Faces is a UK-based charity giving support and information to people with disfigurements (www.changingfaces.org.uk).

Resources

- The standard grading system for rosacea (Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea) is available at www.rosacea.org.
- Under the lash: demodex mites in human diseases, by Lacey N *et al*, reviews the key literature and research experience regarding the pathogenic potential of demodex in inflammatory skin and eye diseases. It is available at www.ncbi.nlm.nih.gov.

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PANEL 4: EXACERBATING FACTORS TO AVOID[1]

- Overly strenuous exercise, hot and humid atmosphere, emotional upset, alcohol, hot beverages and large, hot meals.
- Sun or intense cold or harsh winds.
- Perfumed sunscreens or those containing insect repellents.
- Astringents and scented products containing hydro-alcoholic extracts or sorbic acid.
- Cleansers containing acetone or alcohol.
- Abrasive or exfoliant preparations.
- Vigorous rubbing of the skin.
- Toners or moisturisers containing glycolic acid.
- Medicines that could exacerbate flushing (eg, vasodilator drugs, nicotinic acid, calcium channel blockers and opiates), where possible.

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PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist's CPD portfolio.

1 Do you have any patients with rosacea? Find out what support they would like from pharmacists.
2 Make sure pharmacy staff know which cleansers are mild.
3 Visit rosacea.org and read the answers to frequently asked questions.

Consider making this activity one of your nine CPD entries this year.