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REVIEW

Rosacea

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Abstract

Rosacea is a common cutaneous condition affecting predominantly the face. It is historically characterised into four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular rosacea. This article describes the pathophysiology, clinical features and current treatment options for rosacea, and discusses updated diagnostic criteria. General guidance is required on the need to avoid possible triggers including dietary and environmental triggers. The strongest evidence supports the use of 0.75% metronidazole, topical azelaic acid or topical ivermectin for inflammatory rosacea. Erythema should be treated with brimonidine tartrate gel, oral medication such as beta blockers or vascular laser and light-based therapy. Oral doxycycline 40 mg modified release can be used as monotherapy or in combination with other treatments for recalcitrant disease. Further understanding of the pathogenesis of rosacea could allow identification and targeted avoidance of triggers and the development of new treatment modalities.

Key words: Erythematotelangiectatic, Ocular, Papulopustular, Pathophysiology, Phymatous, Rhinophyma, Rosacea

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Introduction

Rosacea is a chronic inflammatory cutaneous disease, which manifests as facial erythema, flushing, papules, pustules and telangiectasia (Spoendlin et al, 2012). In addition, there can be involvement of the eye, eyelid and soft tissue of the nose (Spoendlin et al, 2012). In 2002, the American National Rosacea Society Expert Committee categorised the disease into four subtypes, namely erythematotelangiectatic, papulopustular, phymatous and ocular rosacea, a framework that remains helpful today when considering treatments. Subtypes frequently overlap and categorisation by phenotypes has been proposed, as outlined in Table 1 (Tan et al, 2017). Rosacea can be associated with devastating psychological sequelae including depression, stigmatisation and low self-esteem (Bewley et al, 2016).

The overall incidence of rosacea diagnoses is estimated to be 1.65 per 1000 person-years in the UK (Spoendlin et al, 2012). Around 80% of rosacea diagnoses are made after the age of 30 years and ocular symptoms are reported in 21% of cases (Spoendlin et al, 2012). A wide prevalence, between 2.2 and 22% (Mikkelsen et al, 2016), has been suggested with a strong female predilection (Mikkelsen et al, 2016). Caucasians and those of Fitzpatrick

Table 1. Diagnostic, major and minor features of rosacea

Diagnostic features	Persistent centrofacial erythema with periods of greater intensity and associations with trigger factors
	Phymatous changes
Major features	Flushing or periodic centrofacial erythema
	Inflammatory papules and pustules
	Telangiectasia
Minor features	Skin burning sensation
	Stinging sensation
	Oedema

From Tan et al (2017)

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skin types one and two (fair skin) appear to be most at risk (Mikkelsen et al, 2016). This article reviews and outlines the pathophysiology, clinical features, differential diagnosis and treatment options available as well as exploring possible avenues for future treatment and research.

Pathophysiology

Those with a family history of rosacea are more likely to develop the condition and a 46–50% genetic contribution has been posited (Mikkelsen et al, 2016).

The pathogenesis of rosacea has not been fully elucidated, but there is evidence to support a multifaceted aetiology with genetic susceptibility and triggers such as pathogens, ultraviolet radiation, diet, temperature extremes, stress, hormones, gastrointestinal disturbances and cardiovascular risk factors (Elewski et al, 2011; Weiss et al, 2017; Searle et al, 2020a, b). Activation of toll-like-receptor-2 (TLR) and transient receptor potential (TRP) ion channels and release of pro-inflammatory cytokines are likely to be involved in the pathogenesis of rosacea (Yamasaki and Gallo, 2011).

Triggers such as alterations in the gut microbiome (small intestinal bacterial overgrowth and *Helicobacter pylori*) have been implicated (Searle et al, 2020b). Dietary triggers such as alcohol, spicy food, cinnamaldehyde-containing foods (tomatoes, citrus fruits, chocolate), hot drinks and histamine-rich foods (aged cheese, wine, processed meats) are other triggers that have also been implicated (Weiss et al, 2017).

Clinical features

The presentation of rosacea has a high inter-individual variability, but considering the historical phenotypes (erythematotelangiectatic, papulopustular, phymatous, ocular rosacea) can be helpful when formulating management plans.

Patients with rosacea typically have centrofacial erythema of the malar cheeks and nose. There may be diffuse redness or prominent telangiectasia (erythematotelangiectatic) (Figure 1). There may be intermittent flushing, and the disease can be triggered by a variety of factors including dietary factors (Searle et al, 2020b) and the environment (such as sunlight, heat, wind). Patients often report sensitive skin ('stinging' or 'burning' sensation), particularly when washing the face or if alcohol-containing topical products (such as gels) are applied (Mikkelsen et al, 2016).

Papulopustular rosacea manifests with transient papules and pustules (Figure 2), as well as facial erythema in the centre of the face, burning, stinging, telangiectasia and raised plaques. This subtype can sometimes be mistaken for acne, but in rosacea comedones do not feature and scarring is rare (Mikkelsen et al, 2016).

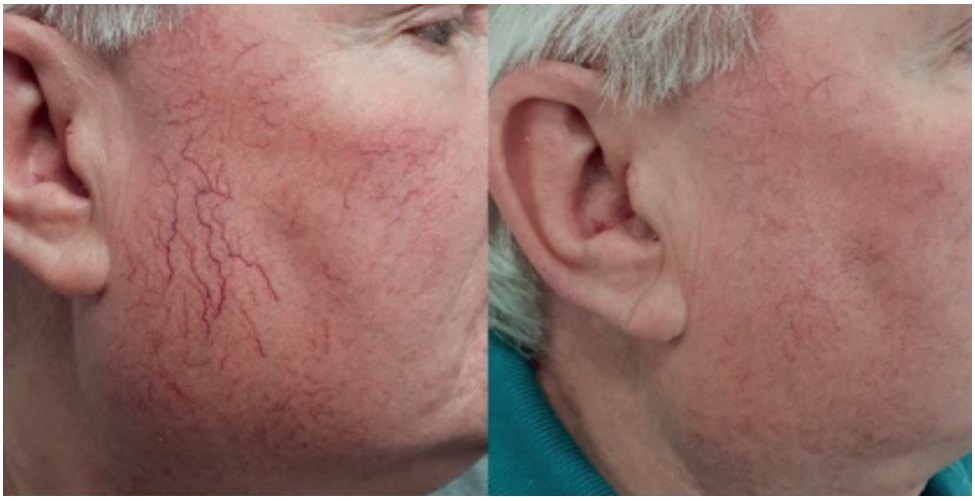

Figure 1. Erythematotelangiectatic rosacea before and after treatment with pulsed dye laser.

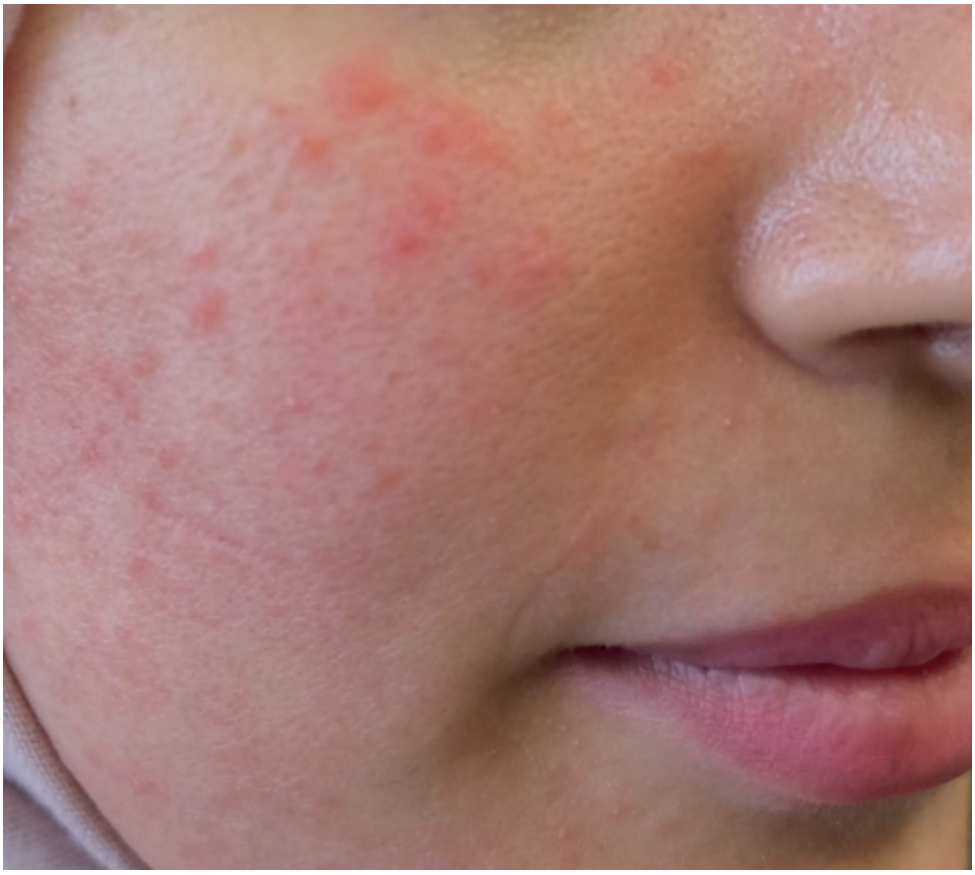

Figure 2. Papulopustular rosacea.

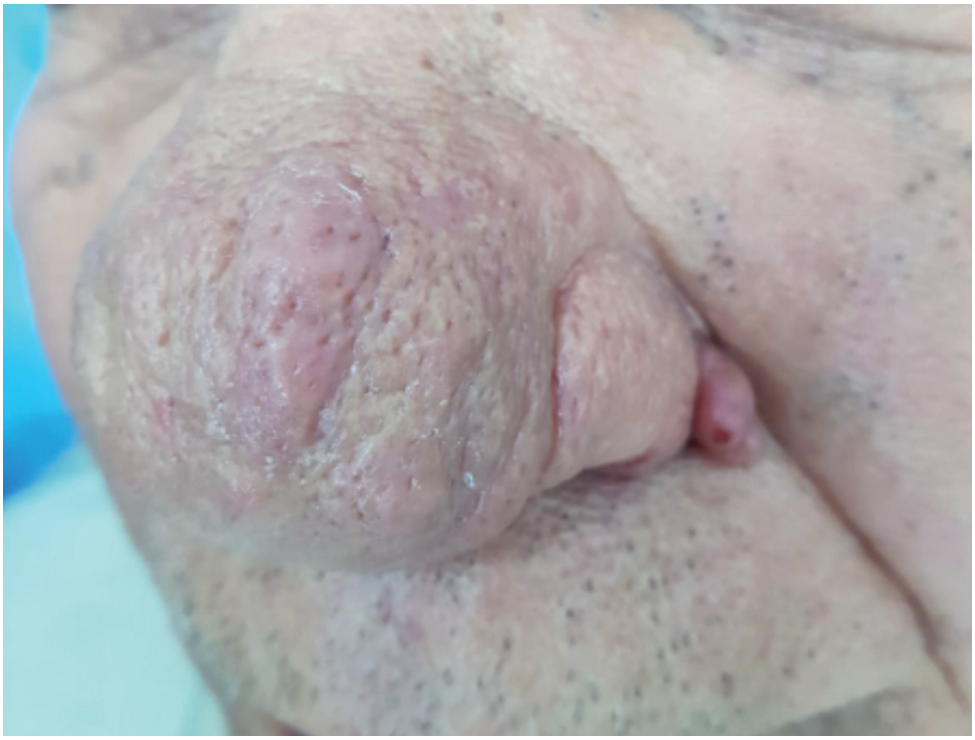

Figure 3. Phymatous rosacea (rhinophyma).

Phymatous rosacea affects men more than women and presents with fibrosis, skin thickening, irregular nasal nodules and often telangiectasia typically on the nose (rhinophyma, Figure 3) (Mikkelsen et al, 2016).

Ocular rosacea has a variety of presentations, from minor ocular disturbances, foreign body sensation, dryness and blurred vision to severe surface damage and inflammatory keratitis. Patients complain of grittiness and often are affected by blepharitis and conjunctivitis. Telangiectasia of both the lid margin and conjunctiva, corneal scars and ulcers as well as chalazion and hordeolum might occur. Ocular rosacea often co-exists with the other subtypes and in up to 20% of patients, ocular signs appear before cutaneous disease (Mikkelsen et al, 2016).

Differential diagnosis

Differential diagnoses vary according to subtype. The differential diagnoses of erythematotelangiectatic rosacea include polycythaemia rubra vera, lupus erythematosus, dermatomyositis, other mixed connective tissue diseases, carcinoid syndrome, mastocytosis, allergic contact dermatitis, arterial hypertension, and ultraviolet-induced cutaneous vascular damage (Powell, 2005). The differential diagnoses of papulopustular rosacea include papulopustular acne, perioral dermatitis, allergic or toxic contact dermatitis, gram-negative folliculitis and eosinophilic folliculitis. The differential diagnoses of ocular rosacea are bacterial, viral (for example, caused by herpes virus), or allergic conjunctivitis, keratoconjunctivitis and trauma (Powell, 2005).

Treatment

Table 2 outlines the treatment options for rosacea.

General advice to all patients

Management of rosacea initially starts with patient education and identification of triggering or exacerbating factors (van Zuuren, 2017). A diary of possible triggers is important to identify dietary, cosmetic and other stimuli possibly involved in the pathogenesis of rosacea (Elewski et al, 2011). Daily sunscreens protecting against ultraviolet (UV) A and UVB light are recommended. In terms of cosmetics, use of non-oily products and cleansers without soaps is advised. Avoidance of waterproof make-up, skin toners, products containing alcohol, peppermint, sodium lauryl sulphate, glycolic acid or exfoliating scrubs is recommended (van Zuuren, 2017).

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea manifests with flushing, persistent facial erythema and telangiectasia. Brimonidine tartrate 0.33% gel is recommended for symptomatic treatment of

Table 2. Treatment options for rosacea

Subtype	Treatment options
All types	Photoprotection, avoid dietary and environmental triggers, avoid alcohol-based topical agents, use of daily sunscreens. Use of non-oily products and cleansers without soaps is advised
Erythematotelangiectatic	Vascular specific lasers or light devices (pulsed dye laser, neodymium-doped yttrium aluminum garnet laser, intense pulsed light)
	Topical brimonidine gel
Papulopustular	Topical agents (metronidazole, azelaic acid, ivermectin, retinoids)
	Oral antibiotics (eg doxycycline modified release)
	Low dose oral isotretinoin (eg 0.25 mg/kg)
Phymatous	Ablative laser devices (CO_2, erbium-doped yttrium aluminium garnet laser)
Ocular	Over the counter ocular lubricants
	Lid hygiene
	Warm compresses

facial erythema and evidence supports the use of laser and light-based therapies for erythema and telangiectasia (Micali et al, 2016). Brimonidine tartrate is a selective alpha-2-adrenergic receptor agonist which acts as a potent vasoconstrictor of blood vessels and may have an anti-inflammatory action (Fowler et al, 2013). Two randomised controlled trials with 533 patients found 0.5% brimonidine tartrate to be effective in reducing persistent erythema (Fowler et al, 2013). Brimonidine has immediate efficacy with improvement reported within 30 minutes of use, peaking from 3–6 hours after use and the effect gradually decreasing after this. Side effects such as erythema, pruritus, burning, flushing and erythema have been reported (Micali et al, 2016).

Other treatments such as oxymetazoline, a partial alpha-2-adrenergic receptor agonist, have weaker vasoconstrictory effects. In two randomised controlled trials (n=885), erythema reduction was significantly greater in the treatment group receiving 1% oxymetazoline hydrochloride than in those who received vehicle therapy (12% vs 6% reduction, P=0.03 in study one and 14% vs 7%, P=0.02) 3 hours after treatment (Draelos et al, 2018; Kircik et al, 2018).

Laser and light-based treatments are used for treating telangiectasia with numerous devices reported to be effective. The 595 nm pulsed dye laser, the 532 nm potassium titanyl phosphate or lithium triborate laser, 1064 nm neodymium-doped, yttrium-aluminium-garnet laser and non-coherent intense pulsed light sources (500–1200 nm) are all potential efficacious treatments which target haemoglobin.

Large randomised controlled trials are required to validate the use of laser and light-based therapy as a monotherapy or in combination treatment with other agents.

Papulopustular rosacea

For the treatment of papulopustular rosacea, topical azelaic acid, topical metronidazole and topical ivermectin are recommended first-line therapies. Ivermectin was a more efficacious treatment than metronidazole in one randomised controlled trials, although there was a relapse of symptoms on treatment cessation with both treatments (Ebbelaar et al, 2018). Two randomised controlled trials involved 1371 patients treated with topical ivermectin or vehicle treatment and found a greater reduction with ivermectin in terms of inflammatory lesions (66% vs 39% in one trial and 70% vs 42% in the other trial (Ebbelaar et al, 2018).

Seven randomised controlled trials have investigated the use of azelaic acid in rosacea. In the largest study, 961 patients with papulopustular rosacea were randomised to receive azelaic acid foam 15% twice daily for 12 weeks or vehicle treatment (Draelos et al, 2015) Azelaic acid foam was more effective than the vehicle as measured by investigator global assessment (Draelos et al, 2015).

In two separate randomised controlled trials (Elewski et al, 2003; Del Rosso et al, 2010), azelaic acid was more efficacious than metronidazole 0.75% gel in reducing mean lesion counts, mean percentage decrease in inflammatory lesions and for erythema. The effectiveness of metronidazole gel seemed to plateau whereas azelaic acid gel persisted to produce improvements at 15-week follow up (Elewski et al, 2003).

More severe disease often requires combinations of topical agents and oral antibiotics; however, there is a paucity of evidence to support use of particular combinations.

Modified release doxycycline (40 mg) is approved by the Food and Drug Administration and the European Medicines Agency (Van Zuuren, 2017) because of its anti-inflammatory properties. Two randomised controlled trials (n=537) treated patients with 40 mg doxycycline, finding significantly greater reductions in lesion count (49% and 61% in the treatment group) compared with placebo (20% and 29%) (Del Rosso et al, 2007; Van Zuuren et al, 2015). Submicrobial 40 mg modified release doxycycline appears to be as effective as the 100 mg doxycycline with fewer side effects (Del Rosso et al, 2008) and 100 mg oral minocycline (van der Linden et al, 2017).

Isotretinoin is a systemic retinoid and is most recognised for its use in treatment of severe acne vulgaris. In lower doses, isotretinoin has been found to be helpful for cases of rosacea as well. Isotretinoin (0.25 mg/kg) was compared with placebo in a 4-month trial for recalcitrant rosacea (n=148) (Sbidian et al, 2016). After 4 months, patient satisfaction scores were 8.89 times higher in the isotretinoin group compared with the placebo group. Isotretinoin improved quality of life scores and 57.4% of those treated with isotretinoin

achieved a 90% reduction in inflammatory lesion count vs 10.4% of the placebo group (relative risk 5·51, 95% confidence interval 2·37–12·83 (P<0·001). Adverse events including eczema, cheilitis, dry skin, gastrointestinal pain, myalgia and dry eyes were reported by 69% of the treatment group vs 44% of the placebo group (Sbidian et al, 2016).

A further study compared low dose isotretinoin 0.3 mg/kg and oral doxycycline 100 mg over a 2-week treatment period (subsequently tapered to 50 mg) (n=299). A slight difference in support of isotretinoin was reported in patient's self-assessment, good-to excellent improvement scores, lesion count reduction and physician's assessment. Adverse events reported were not different between groups (Gollnick et al, 2010). Isotretinoin is highly teratogenic and double contraceptive techniques and monthly pregnancy tests are required (Powell, 2005; Reinholz et al, 2013).

Phymatous rosacea

For fibrotic phymatous lesions, ablative laser therapy or surgical therapy (including radiofrequency) is used as first-line treatment. Topical retinoids, oral doxycycline, oral tetracycline or oral isotretinoin have been suggested for early-stage disease.

In a study of 124 patients who had carbon dioxide laser for rhinophyma, 77% of patients rated their satisfaction levels to be at least seven out of ten and 92% of patients stated that they would recommend this treatment to others suffering from rhinophyma (Madan et al, 2009). Studies with larger numbers are required to support using lasers in rhinophyma with longer follow-up periods. Additionally, caution is required in different skin types with risk of dyspigmentation and scarring in darker skin types (Madan et al, 2009).

Ocular rosacea

For ocular rosacea, eyelid hygiene is very important with warm water and artificial tears. Ciclosporin eye drops might be effective for improving quality of life scores, although these should not be used for active ocular infections (Schecter et al, 2009). Topical metronidazole or fusidic acid are other treatment options. Severe disease might warrant treatment with oral doxycycline (40 mg or 100 mg). If this proves ineffective, referral to an ophthalmologist is required to rule-out sight-threatening disease (Powell, 2005; Schecter et al, 2009; Reinholz et al, 2013). Omega-3 fatty acid capsules (containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) have improved subjective dry eye symptoms and measures of eye dryness (Bhargava et al, 2016).

Overall, ocular rosacea is a chronic condition requiring long-term treatment. Therefore, given the side-effect profile of systemic doxycycline, topical ciclosporin may be more appropriate for long-term treatment and has also proven to be more effective in symptomatic relief and for improving tear break-up time scores (Schecter et al, 2009).

Future avenues for research and treatments

In terms of future treatment, greater understanding of trigger factors for rosacea will allow for better treatment options. Small intestinal bacterial overgrowth and *H. pylori* are also thought to be associated with the development of rosacea (Searle et al, 2020b). Patients with cardiometabolic syndrome and the associated pro-inflammatory phenotype frequently present with rosacea. Emerging clinical evidence supports the relationship between rosacea and cardiometabolic syndrome, hypertension and obesity (Searle et al, 2020a).

Research has highlighted the role of interleukin-17 (IL-17) in the development and progression of rosacea. IL-17 inhibitors are used in inflammatory conditions such as psoriasis and psoriatic arthritis and might be of value in the future treatment of papulopustular rosacea, with randomised clinical trials required to investigate this further (Amir Ali et al, 2019).

Conclusions

Rosacea is a common dermatosis with a broad range of symptoms including erythema, telangiectasia, papules, pustules, phymatous alterations and ocular dysfunction. Many patients present with overlapping features of the different categories and therefore treatment

Key points

- Rosacea can present with various symptoms including erythema, telangiectasia, papules, pustules, phymatous alterations and ocular dysfunction.
- The aetiology of rosacea is not fully understood but dietary, metabolic or cardiovascular factors might have a role.
- First-line topical treatments include topical metronidazole, azelaic acid and ivermectin.
- Systemic medication with doxycycline 40 mg modified release can be used as monotherapy or possibly in combination with topical treatments.

must be personalised, often requiring combination therapy. Education about trigger avoidance in terms of diet and keeping a diary to identify potential triggers are simple steps to help treat this condition. Photoprotection is also essential using sunscreen with a sun protection factor of at least 30. First-line topical treatments for inflammation include metronidazole, azelaic acid and ivermectin. Brimonidine tartrate gel or oxymetazoline cream are topical agents that can be used to treat erythema in addition to laser and light-based interventions. Systemic medication with doxycycline 40 mg modified release can be used as monotherapy or possibly in combination with topical treatments.

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Conflicts of interest

The authors declare no conflicts of interest.

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