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REVIEW ARTICLE

Ocular rosacea: The often-overlooked component of rosacea

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Abstract

Ocular rosacea is a chronic inflammatory condition that affects the eyes and periocular skin as part of the broader cutaneous rosacea skin disease. Cutaneous rosacea is common, affecting approximately 5.5% of the global population, where up to 72% of patients will develop ocular involvement either before or after the cutaneous disease. Clinical features of ocular rosacea include Meibomian gland disease, blepharitis and conjunctivitis. Ocular rosacea reduces quality of life through various potential mechanisms including anxiety, social withdrawal and physical discomfort. If left untreated, ocular rosacea can reduce visual acuity and in severe cases, vision loss. Several topical and systemic treatment options are available, with efficacies based on their anti-inflammatory properties. This review focuses on the clinical features of ocular rosacea, differential diagnoses and treatment options with the aim of aiding clinicians involved in the care of rosacea patients to better identify onset of the ocular manifestations of rosacea and prevent its severe complications.

KEYWORDS

antibiotics, anti-inflammatory, ocular rosacea, physical modalities

INTRODUCTION

Ocular rosacea is a chronic inflammatory disease that affects the eyes and the skin surrounding them. This condition is a manifestation of the broader rosacea skin disease, involving three clusters of cutaneous symptoms: telangiectasias (often associated with flushing/blushing), papules/pustules (papulopustular rosacea) and thickening of the nose due to a combination of fibrosis, sebaceous hyperplasia and lymphedema (rhinophyma). Studies on the prevalence of rosacea report a range of 0.1%–22%, with a recent meta-analysis estimating the global prevalence to be 5.5%.[1–13] While rosacea is most commonly observed in patients over the age of 30, it can also occur in children, with a study from China reporting a prevalence of 0.97% among adolescents within 12–20 years of age.[14] Although rosacea is more common in women, ocular rosacea affects both sexes equally, with ocular manifestations occurring in 58%–72% of rosacea patients. In 80% of rosacea cases, cutaneous features precede any ocular involvement.[15]

Due to rosacea affecting the facial region, an individual's physical appearance can be impacted substantially. As a result, psychosocial impacts contribute a

large portion to the burden of disease associated with rosacea. The red enlarged nose, characteristic of phymatous forms of rosacea, is often associated with alcohol abuse. Whereas the bloodshot eyes of ocular rosacea can be associated with alcohol or drug abuse. Rosacea patients often report lowered self-esteem, anxiety and avoidance of social interactions.[16,17]

Given the profound psychosocial impacts and potential for decreasing patient quality of life, it is important for early recognition and correct diagnosis of rosacea to facilitate appropriate treatment. While the cutaneous forms of rosacea are frequently recognized, ocular rosacea remains more often undiagnosed. This issue of underdiagnosis is likely multifactorial. Physicians making a diagnosis of rosacea often focus on cutaneous symptoms and overlook inquiring about ocular symptoms. Another factor could be that patients primarily focus on their facial appearance and do not bring ocular symptoms to the attention of their physician. Finally, the clinical features of ocular rosacea are nonspecific, which may lead to misdiagnosis.[18] The aim of this review is to provide clinicians involved in the care of rosacea patients with information regarding the features of ocular rosacea, differential diagnoses and treatment options.

PATHOGENESIS

Rosacea pathogenesis is a complex topic that is not fully understood but is believed to be a multifactorial process involving several factors including neurovascular dysregulation, innate immune dysregulation, micro-organisms and UV radiation.

Central to neurovascular regulation are the transient receptor potential channels (TRPs), which are calcium channels with sensory roles. TRPs respond to several stimuli, many of which are common rosacea triggers, including heat and capsaicin.[19,20] Activation of TRPs can lead to burning sensation and vasodilation, which may play a role in the flushing and blushing observed in rosacea.[21] Several TRPs are found to be upregulated in rosacea skin.[22]

Innate immune system dysregulation in rosacea revolves around aberrant cathelicidin (LL-37) expression, toll-like receptor 2 (TLR2) signalling and inflammasome activation. TLR2 signalling and LL-37 expression leads to degradation of extracellular matrix by metalloproteases, production of reactive oxygen species and pro-inflammatory cytokines, all of which contributes to the chronic skin damage and inflammation observed in rosacea.[23–25] Inflammasomes are activated by cellular damage and further release pro-inflammatory cytokines and promotes angiogenesis, which may contribute to the enhanced vascularization observed in rosacea skin.[26,27] UV exposure can not only directly cause damage to the superficial cutaneous vasculature, collagen and elastin, they also upregulate expression of matrix metalloproteases, resulting in further tissue damage and inflammation.[28–30]

Demodex folliculorum mites are common inhabitants of human skin implicated in rosacea pathogenesis by the observation that they have a preference for inhabiting regions of the face most commonly affected by rosacea and their densities correlate positively with the appearance of rosacea features.[30] The evidence for the involvement of *D. folliculorum* involvement is strongest in the papulopustular rosacea subtype, where high *D. folliculorum* density is found in 98.6% of patients on biopsy. In lower densities, *D. folliculorum* is believed to induce immunotolerance to promote its own proliferation. However, at higher densities, the immunogenic actions of the mite exceeds its immunosuppressive effects, resulting in the formation of inflammatory papules and pustules.[31] Furthermore, eradication of the mites with acaricidal agents including ivermectin and tea tree oil has demonstrated clinical efficacy in treating papulopustular rosacea.[32]

Clinical features of cutaneous rosacea

Given that ocular rosacea, if left untreated, can affect an individual's quality of life, and can also lead to severe vision impairment, it is important that patients with ocular rosacea are correctly diagnosed. While ocular rosacea primarily affects the Meibomian glands, many other features of ocular rosacea are nonspecific and can be difficult to distinguish from other ocular diseases without observation of cutaneous symptoms. The clinical features of the three cutaneous rosacea subtypes are briefly described here.

The erythrotelangiectatic subtype is characterized by persistent erythema and flushing of the central facial region, sparing the periocular region. Although uncommon, the erythema can extend past the central facial region, to areas including the upper trunk and neck. Telangiectasias are commonly observed, but not diagnostic.[33] The papulopustular subtype is characterized by erythematous papules and pustules and persistent erythema in the central facial region, sparing the periocular area.[34] Lastly, Phymatous rosacea (rhinophyma) is characterized by localized thickening of the skin along with surface nodularity that typically affects the nose.[33] It is important to note that several of these subtypes may be present concurrently. A summary of the subtypes is provided in Table 1.

TABLE 1 Rosacea subtypes and major characteristics defining each subtype.

Rosacea subtype	Major characteristics
Flushing/blushing (erythrotelangiectatic)	Flushing of centrofacial region Persistent erythema of centrofacial region
Papulopustular (inflammatory)	Erythematic papules and pustules persistent erythema of centrofacial region with an absence of associated comedones
Phymatous (rhinophyma)—Enlarged nose most common	Localized skin thickening due to a combination of fibrosis, sebaceous hyperplasia and lymphedema
Ocular	Blepharitis—Red swollen, with scale/crust and marginal telangiectasia Conjunctivitis—Pink eye and if severe there is a red discoloration Corneal Keratitis—Local inflammation Meibomian gland disease

TABLE 2 Proposed set of diagnostic criteria for ocular rosacea.

Early features	Advanced features
Blepharitis	Corneal ulcer
Centrofacial erythema and flushing	Corneal perforation
Persistent and uncontrolled dryness, burning and stinging sensations in eyes	Ocular telangiectasia
Keratitis	
Meibomian gland dysfunction	

Note: Definite ocular rosacea is indicated by ≥2 early features or ≥1 advanced feature. Possible ocular rosacea is indicated by centrofacial erythema and one early feature. Adapted from Andreas et al.[36]

Clinical features of ocular rosacea

Given that the clinical features of ocular rosacea are nonspecific and that diagnosis is reliant on clinical observations, it can be difficult to make a correct diagnosis and many differential diagnoses must be considered. In general, the major features of ocular rosacea involve manifestations of the eyelids, cornea, conjunctiva, iris and ciliary body.[35] A diagnostic criteria is shown in Table 2. Clinical presentation of ocular rosacea is provided in Figures 1–6.

Manifestations of the eyelids

Ocular rosacea primarily affects the Meibomian glands, resulting in Meibomian gland disease characterized by a pathologic change in either the quantity or composition of the secreted meibum. Patients may experience burning, dryness, foreign body sensation and inflamed eyelids. Clinical features include telangiectasias of the lid margin on slit-lamp examination, inspissation (increasing viscosity) of the Meibomian glands and often, thickening of the lid margins. The health of Meibomian glands can be assessed by

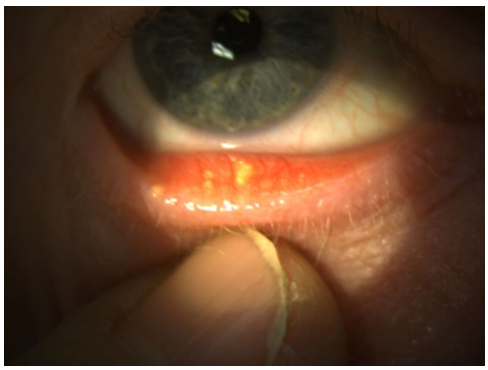

FIGURE 1 Meibomian gland disease characterized by telangiectasia crossing the lid margin, thickening of the lid margin and inspissation of the Meibomian glands.

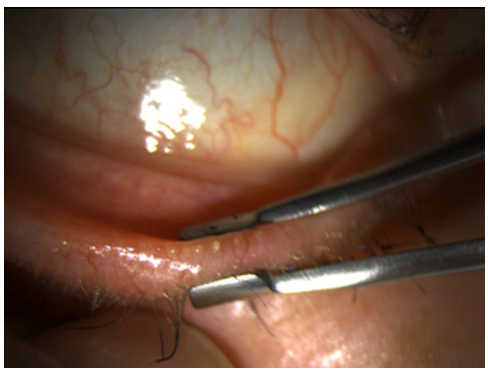

FIGURE 2 Lid expression of inspissated Meibomian glands. Conjunctival injection can be observed.

newer imaging techniques which utilize infrared meibomography, a specialized imaging study developed exclusively for the purpose of directly visualizing the morphology of the Meibomian glands. Chronic blepharitis is a very common manifestation of ocular rosacea.[37] Other common irregularities include chalazion (red bump on eyelid- blocked Meibomian gland), hordeolum (stye or infected gland),

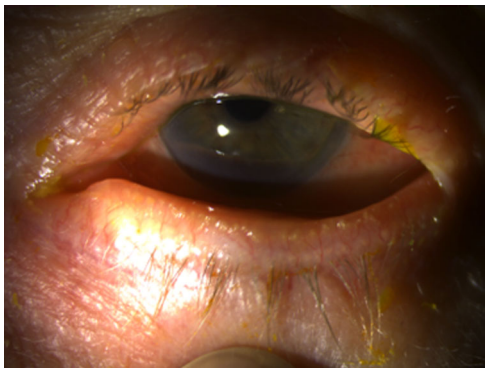

FIGURE 3 Inspissated Meibomian glands with telangiectatic vessels on lower eyelid.

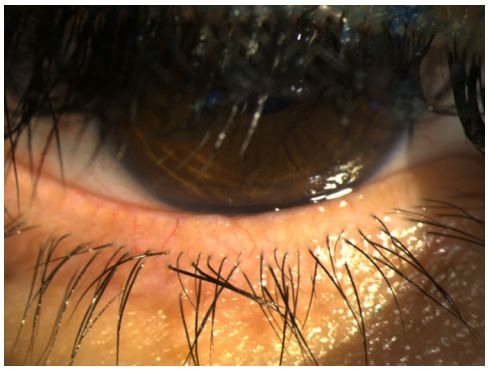

FIGURE 4 Lid margin telangiectasia.

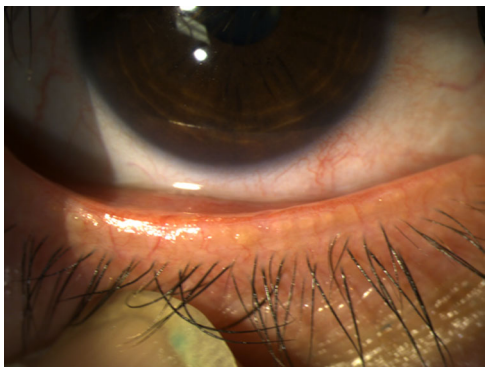

FIGURE 5 Inspissation of Meibomian glands with lid margin telangiectasia and conjunctival hyperemia.

crusts, scales and telangiectasias.[38] According to the 2019 guidelines set by the global ROSacea COnsensus (ROSCO) panel, the presence of lid margin telangiectasia and blepharitis are the most important eyelid manifestations to consider. For assessing severity of lid margin telangiectasia, the density and degree of vascularization, and Meibomian gland dysfunction must be taken into account. For blepharitis, the degree of inflammation, pain and swelling must be considered.[35]

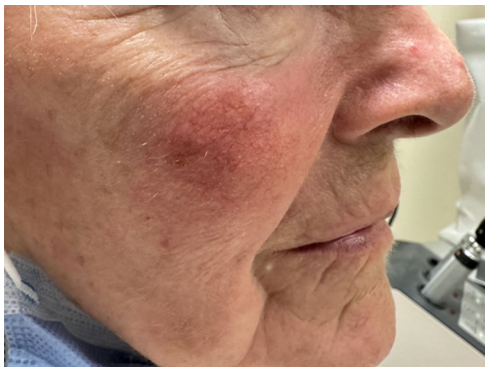

FIGURE 6 Cutaneous rosacea with persistent erythema and telangiectasia on the right cheek.

Manifestations of the conjunctiva

Chronic conjunctivitis with hyperemia (pink eye) is the most common manifestation involving the conjunctiva.[37] Papillary reactions, granulomas, phlyctenule (nodular inflammation) can also be observed.[39] Based on 2019 ROSCO guidelines, conjunctivitis is the most relevant conjunctival manifestations to consider. In assessing severity, the presence and degree of hyperemia and foreign body sensation must be accounted for.[35]

Manifestations of the cornea

Superficial corneal neovascularization with lipid deposits are the most common manifestation of the cornea.[37] Evaporative dry eye, pannus formation (vascular ingrowth from limbus onto peripheral cornea), keratitis (inflammation), scarring and lipid deposits are some of the other common irregularities that may be observed involving the cornea.[39,40] ROSCO 2019 guidelines indicate that keratitis is the most important corneal manifestation to consider. Keratitis associated with rosacea typically affects the inferior cornea.[41] Severity is determined based on location (e.g., superficial punctate, interstitial), degree of inflammation, pain and foreign body sensation.[35] It is important to note that corneal complications may result in reduction in visual acuity and in very rare situations, severe ulcerations can result in blindness.[33,38]

Manifestations of the uvea

Anterior uveitis (inflammation inside the eye) is the most relevant manifestation of the uvea based on the 2019 ROSCO guidelines. When assessing severity, cell count in the anterior chamber aqueous humour and severity of

flare must be considered.[35] This is an exceedingly rare occurrence and is commonly secondary to keratitis.

Symptoms of ocular rosacea

While it is important for physicians to recognize the clinical signs of ocular rosacea, the cutaneous forms of rosacea often precede ocular manifestations.[42] Thus, it is important for rosacea patients to be familiar with the symptoms of ocular rosacea so they can alert their physicians of new ocular involvement. The most common symptoms of ocular rosacea include redness, tearing, itchiness, burning, foreign body sensation, photophobia and blurred vision.[43] Patients may not necessarily experience these symptoms in any specific order or combination. These symptoms may result in patients experiencing constant ocular discomfort, reduced aesthetic appeal and in rare circumstances, loss of vision, leading to notable reduction in quality of life. An overview of ocular rosacea symptoms and potential impacts on patients is provided in Figure 7.

Differential diagnoses

The clinical features of ocular rosacea can vary in severity and often overlap with features in other ophthalmologic conditions. To further complicate matters, other ophthalmologic conditions can also vary in clinical presentation. Ocular rosacea may share the same clinical features or even coexist with these other ophthalmologic conditions. While the facial cutaneous features of rosacea can often be used as a distinguishing factor, it is not always reliable since some of these alternative diagnoses can coexist with rosacea and 20% of rosacea patients exhibit ocular symptoms before their cutaneous symptoms.[44] It is important to be familiar with the similarities and differences between ocular rosacea and other similarly presenting ophthalmologic conditions to prevent misdiagnosis. A summary of differential diagnoses is provided in Table 3.

Types of blepharitis

Staphylococcal blepharitis

Staphylococcal blepharitis is caused by colonization of the eyelid margin, most commonly by *Staphylococcus aureus*. Staphylococcal blepharitis is quite common, especially in warmer countries. For example, the prevalence in India has been reported to be as high as 61%.[45] Interestingly, staphylococcal blepharitis exhibits sexual preference, with 80% of patients being female with a mean age of 42 years.[46]

The main clinical features of staphylococcal blepharitis include burning, itching, photophobia and a sensation of grittiness. Lid margins also present with hyperemia and hard crusting scales that form collarettes around the lashes.[46] While these features can also occur in ocular rosacea, the cutaneous changes of rosacea are not observed in staphylococcal blepharitis.[37]

Meibomian gland dysfunction

Meibomian gland dysfunction is an obstruction of the Meibomian gland believed to be caused by

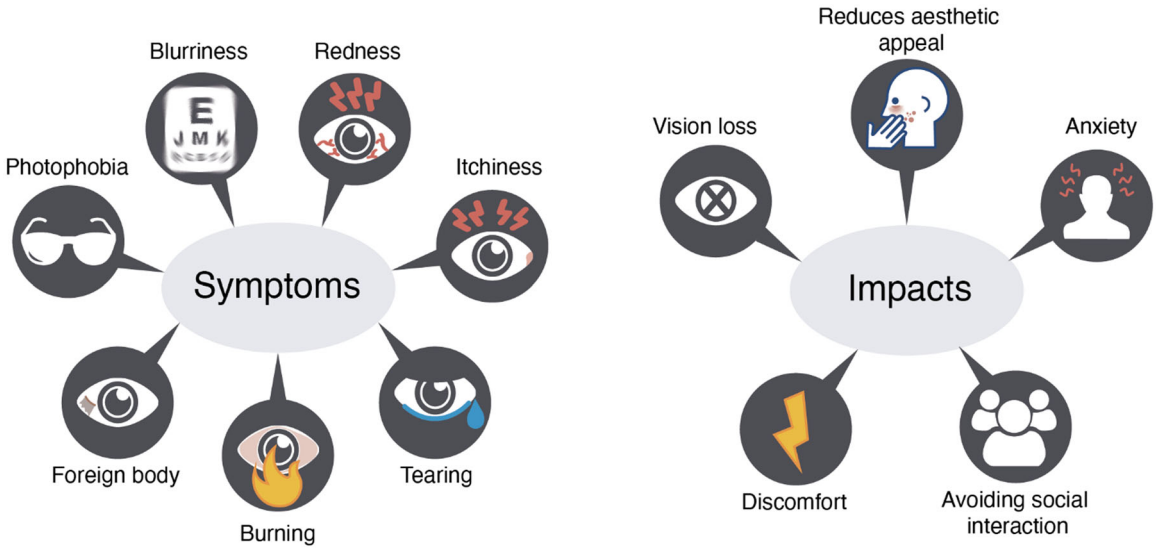

FIGURE 7 Diagrammatic representation of potential ocular rosacea symptoms and impacts on patients.

TABLE 3 Differential diagnoses of ocular rosacea and clinical presentations that differentiate them from ocular rosacea.

	Differentiating features	
Ophthalmic condition	**Observed in ocular rosacea**	**Not observed in ocular rosacea**
Staphylococcal blepharitis	Conjunctival phlyctenules (nodules) Rosacea facial cutaneous changes	-
Meibomian gland dysfunction	Erythema of lid margins, styes or chalazia Rosacea facial cutaneous changes	-
Seborrheic blepharitis	Rosacea facial cutaneous changes	Cutaneous changes not associated with rosacea
Seasonal and perennial conjunctivitis	Rosacea facial cutaneous changes	Ocular pruritis Seasonal exacerbation
Atopic keratoconjunctivitis	Rosacea facial cutaneous changes	Keratoconus Papillary hypertrophy
Nonchlamydial bacterial conjunctivitis	Rosacea facial cutaneous changes	-
Chlamydial conjunctivitis	Rosacea facial cutaneous changes	Entropion Possible history of change in sexual partner Tarsal follicles
Viral conjunctivitis	Rosacea facial cutaneous changes	Conjunctival injection Tarsal conjunctiva membrane formation Tarsal conjunctiva pseudo-membrane formation
Episcleritis	Discharge Photophobia Rosacea facial cutaneous changes	More often unilateral Usually acute onset
Iritis	Rosacea facial cutaneous changes	Most cases unilateral
Microbial keratitis	Rosacea facial cutaneous changes	-
Peripheral ulcerative keratitis	Rosacea facial cutaneous changes	-
Keratoconjunctivitis sicca	Rosacea facial cutaneous changes	-

Note: Note that due to the nonspecific presentation of ocular rosacea signs and symptoms, the differentiating features may not always be present.

hyperkeratinization of the ductal epithelium.[46] The global prevalence is estimated to be approximately 36%, with men exhibiting greater susceptibility.[47] Meibomian gland dysfunction may be primary and occur in absence of other local or systemic disease, or may be secondary to other diseases, including common skin conditions such as rosacea, atopic dermatitis and psoriasis.[48]

The clinical features of Meibomian gland dysfunction include irritation, redness, increased viscosity of meibum (lipid rich) secretions, chalazia and reduced tear film breakup time.[49] These features are all common to ocular rosacea, leaving only the facial cutaneous changes associated with rosacea as the differentiating factor. However, this is complicated by the fact that 40%–50% of Meibomian gland dysfunction patients also have rosacea.[50]

Seborrheic blepharitis

Seborrheic blepharitis originates from a dermatological condition referred to as seborrhea, whose pathogenesis is believed to involve the pathological proliferation of *Malassezzia* yeast.[50,51] The prevalence of seborrheic blepharitis is higher in older age groups, with no sexual preference.[52]

The clinical presentation of seborrheic blepharitis is similar to staphylococcal blepharitis, except the scaling is oilier, less inflammation and tends to involve characteristics of Meibomian gland dysfunction as well.[53] Given the dermatological origin of seborrheic blepharitis, differentiation with ocular rosacea is based on observations of cutaneous manifestations that are not observed in rosacea. For example, seborrhea can present with erythematous plaques or yellow scales in facial and extrafacial regions.[51]

Types of conjunctivitis

Allergic conjunctivitis

Allergic conjunctivitis is caused by an IgE-mediated inflammatory response induced by exposure to allergens.[54]

The prevalence of allergic conjunctivitis is estimated to range between 6% and 30%, with children making up 30% of all cases.[55]

The mildest forms of allergic conjunctivitis are seasonal and perennial allergic conjunctivitis, which only differ in the periodicity of symptoms. The main clinical features include ocular pruritus, conjunctival hyperemia and tearing.[56] There are several factors that may be useful in distinguishing ocular rosacea from allergic conjunctivitis. The symptoms of ocular rosacea do not have a periodic pattern of appearance and is not IgE mediated and thus, allergic tests may be of diagnostic utility.

Atopic keratoconjunctivitis is the most severe form of allergic conjunctivitis, requiring prompt treatment to prevent loss of vision. It originates from a dermatological condition called atopic dermatitis, which is caused by a combination of genetic predisposition and immune dysregulation induced by allergens. Some clinical features of atopic keratoconjunctivitis including conjunctival hyperemia and stinging are common to ocular rosacea. Other features that may be present including papillary hypertrophy (inside of the eyelid is red, swollen and irritated), punctate corneal erosions, and epithelial filaments can serve as distinguishing factors.[57] However, punctate corneal erosions and epithelial filaments can be observed in dry eye independent of the cause as well.[58,59]

Bacterial conjunctivitis

The cause of bacterial conjunctivitis varies by age, where *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most common causes in children, with *H. influenzae* and *Staphylococcus aureus* being the most common causes in adults.[60]

Clinical features of bacterial conjunctivitis include sticky eyelids, conjunctival hyperemia, purulent secretions and burning.[61] These symptoms may also be present in ocular rosacea, leaving the cutaneous features of rosacea as the main differentiating feature. However, a bacterial swab for microscopic examination and culturing the conjunctiva to identify the common bacterial species that tend to cause bacterial conjunctivitis remains an option as well.

While most cases of bacterial conjunctivitis are acute and typically resolve in 1–2 weeks, those caused by *Chlamydia trachomatis* infection tend to be more chronic in nature.[60] Clinical features are similar to those of nonchlamydial conjunctivitis, but also exhibit additional features including tarsal follicles (round collections of lymphocytes most prominent on the inferior fornix), trichiasis (eyelashes growing inward toward the eye) and entropion (eyelid turns inward).[62] With the exception of trichiasis, which can occur in rosacea-associated blepharitis, the other features may serve as distinguishing features.

Viral conjunctivitis

Viral conjunctivitis is most commonly caused by adenovirus strains. Viral conjunctivitis accounts for the majority of acute conjunctivitis cases.[63] The clinical features of viral conjunctivitis are similar to those of nonchlamydial bacterial conjunctivitis, except the secretions are watery. Diffuse conjunctival injection may be unilateral or bilateral and are usually acute in onset. These typically begin in one eye and the involves the other eye after 3–5 days. However, pseudo-membranes or membranes form in the tarsal conjunctiva in some cases and can serve as a distinguishing factor.[64]

Episcleritis

Most cases of episcleritis (unilateral or bilateral inflammation of the subconjunctival eyewall layer, which is between the conjunctiva and sclera) are idiopathic, with a minority being associated with systemic inflammatory conditions including rheumatoid arthritis and Crohn's disease. Episcleritis is more common in young to middle aged adult groups, with a sexual predilection towards women.[65]

There are two forms of episcleritis, diffuse and nodular, with the diffuse form making up 70% of episcleritis cases.[66] The clinical presentation of both forms involve redness and discomfort, but nodular episcleritis will additionally present with nodules.[65] Episcleritis patients do not experience photophobia or discharge, and approximately 65% of cases are unilateral.[67] These features can serve as distinguishing factors. However, it is important to note that episcleritis (and scleritis) can also be manifestations of rosacea.[41]

Iritis

Iritis, also referred to as anterior uveitis, can be caused by a variety of different factors including trauma, infection or autoimmunity, but is most often idiopathic in nature. While there are other forms of uveitis, iritis is the most commonly diagnosed and does not exhibit any sexual predilection.[68]

Iritis is an inflammation of the iris and/or ciliary body, with clinical features including photophobia, redness, ciliary injection and blurred vision. While these

are all features common to ocular rosacea, iritis is typically unilateral.[69] The bilateral presentation of ocular rosacea and the facial features of rosacea can serve as distinguishing factors. However, it is important to note that iritis may be a presentation of ocular rosacea, although uncommon.

TYPES OF KERATITIS

(A) Microbial keratitis (infection of the cornea or coloured portion of the eye).

Microbial keratitis is most commonly caused by bacterial or fungal infection and may be associated with wearing contact lens. *Staphylococcus* strains cause the majority of bacterial keratitis. Fungal keratitis is far less common, where *Fusarium* species are the most common cause.[70]

The clinical features of bacterial keratitis include conjunctival hyperemia, purulent secretions, photophobia, corneal infiltrates and blurred vision.[71] These are all common to ocular rosacea. Infectious keratitis is very painful and usually of acute onset. These features help to distinguish this from keratitis caused by ocular rosacea, which is typically chronic with periodic acute episodes. Corneal scrapings could be used for microbiology testing to aid in distinguishing as well.

Fungal keratitis share similar clinical presentation as bacterial keratitis, but may be more indolent.[71] As such, the facial cutaneous features of rosacea and microbiology testing remain the distinguishing factors.

(B) Peripheral ulcerative keratitis (ulcer with inflammation of the cornea).

While peripheral ulcerative keratitis can be caused by infectious factors, it is more commonly caused by noninfectious conditions, including rheumatoid arthritis.[72] Peripheral ulcerative keratitis is a serious but rare condition that affect men and women equally.[73]

The typical clinical presentation of peripheral ulcerative keratitis consists of a crescent shaped corneal ulcer, photophobia and redness.[73] Unfortunately, these signs may also be present in ocular rosacea, particularly in severe forms, leaving the facial cutaneous features of rosacea as the distinguishing factor.

KERATOCONJUNCTIVITIS SICCA

Keratoconjunctivitis sicca, also referred to as dry eye disease, is caused by a combination of chronic inflammation and lacrimal functional unit dysfunction, resulting in insufficient production or accelerated evaporation of tears.[74] Keratoconjunctivitis sicca is a very common condition with a prevalence ranging between 5% and 35% in various age groups, with older age groups and women being more susceptible.[75]

Clinical presentation of keratoconjunctivitis sicca include dryness, redness, foreign body sensation, burning and itching, all of which can also be experienced by ocular rosacea patients.[76] A Schirmer test (paper strips placed on the eye treated with local anaesthetic) can demonstrate aqueous tear deficiency and help support a diagnosis of keratoconjunctivitis sicca. Patients with ocular rosacea frequently present with aqueous tear deficiency, referred to as an evaporative tear deficiency.[37,77] The Meibomian glands secrete meibum to prevent evaporation of the tear film. However, Meibomian gland dysfunction is often associated with ocular rosacea, resulting in a more rapid evaporation of the tear film. As such, the cutaneous features of rosacea remain the main distinguishing factor.

Ocular rosacea treatments

Like the cutaneous subtypes of rosacea, there is no cure for ocular rosacea. Treatments centre on controlling signs and symptoms. While there are a variety of treatments available, patient education remains vital. In particular, it is important to counsel patients on the chronic nature of the condition and the importance of reducing exposure to environmental factors that may trigger flare-ups. Unfortunately, environmental triggers specific to ocular rosacea remain understudied, but likely share notable overlap with the triggers of cutaneous rosacea, which are summarized in Table 4.

An ocular rosacea treatment algorithm has recently been developed by an expert panel of Canadian dermatologists (Figure 8). The algorithm proposes the use of conservative eye care measures and in more severe or resistant cases, in conjunction with pharmaceutical interventions and consultation with ocular specialists.[78] A table of ocular rosacea features that require referral to ophthalmology has been provided (Table 5).

Here, the safety and efficacy of ocular rosacea treatments will be discussed, with the highest level of evidence supporting these treatments being indicated in brackets. Some of the treatments discussed are not outlined in the Canadian ocular rosacea treatment guidelines, but nevertheless have demonstrated efficacy. A summary of ocular rosacea treatments is provided in Table 6.

Conservative eye care methods

With Meibomian gland dysfunction and blepharitis being the most common features of ocular rosacea experienced by

TABLE 4 Common triggers of rosacea.

Trigger factor category	Examples
Environmental	Hot/cold temperatures, humidity, sun, wind
Food/beverage	Alcohol, hot foods/beverages, spicy food
Pharmacological	Ingredients containing: Alcohol, acetone, fragrances, vasodilators, witch hazel
Physical	Exercise, heavy lifting
Psychological	Anxiety, emotional stress

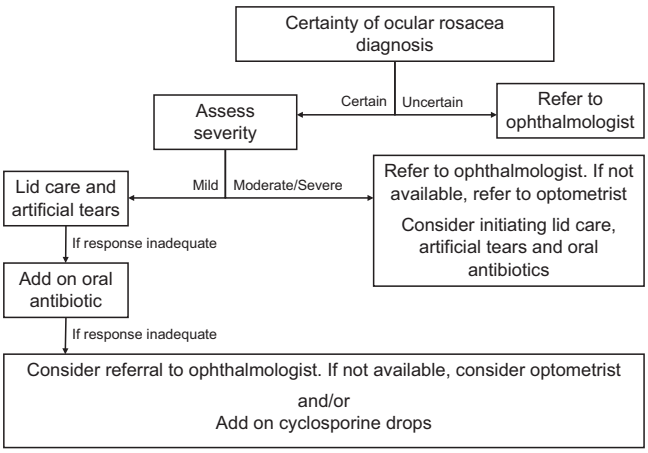

FIGURE 8 Ocular rosacea treatment algorithm.

TABLE 5 Features of ocular rosacea requiring referral to an ophthalmologist.

Category	Condition/features
Persistent or worsening ocular symptoms that reduce patient quality of life	Conjunctival hyperemia Decreased visual acuity Foreign body sensation Symptoms of meibomian gland dysfunction including dryness, grittiness and increased tearing Ocular pain Photophobia
Evidence of corneal involvement	Keratitis Perforation Ulceration
Recurrent eye or eyelid infections of moderate-advanced severity	Blepharitis Chalazia Conjunctivitis Styes

TABLE 6 Summary of therapies demonstrating efficacy in treating ocular rosacea.

Treatment category	Treatments
Conservative management	Artificial tears (nonpreserved tears recommended) Lid hygiene (see conservative eye treatment) Oral omega-3/6 supplementation
Topical	Azithromycin Corticosteroids Cyclosporine Ivermectin Metronidazole Pimecrolimus and Tacrolimus
Systemic	Doxycycline Ondansetron Oxytetracycline/tetracycline
Procedural	Intense pulsed light Lipiflow

patients, the first line of treatment for mild cases consists of the use of conservative eye care strategies to improve the flow of meibum and improve lid hygiene. Recommended methods include preservative-free artificial tears to relieve dryness and lid hygiene. Lid hygiene is recommended through the use of warm compresses for 10 min BID followed by cleaning the lid margins to remove mucous debris.

Supplementation with omega-3 acids may be beneficial in improving Meibomian gland dysfunction, dryness and blepharitis, but the evidence is inconsistent.[79,80] In a randomized placebo-controlled study, patients with Meibomian gland dysfunction and blepharitis supplemented with 1000 mg flaxseed oil TID demonstrated marked improvements in symptoms at the end of the 1-year trial compared to placebo. However, the sample size of this trial was small. Of the 38 patients recruited, only 30 reached the primary endpoint.[81] The use of omega-6 supplementation has also been studied in trials, but results were also inconclusive.[82–84]

TOPICAL THERAPIES

Topical azithromycin

Azithromycin is a macrolide antibiotic available as 1.0% and 1.5% that has shown efficacy in treating ocular rosacea likely through its ability to inhibit production of inflammatory cytokines. Topically applied azithromycin features rapid absorption and a long half-life, requiring less frequent dosing and is a viable option for patients who want to avoid adverse reactions associated with taking antibiotics systemically.[85]

In one study, 16 pediatric patients underwent 3-day-long treatment with 1.5% azithromycin drops twice-daily three times per month in the first 2 months, which were then tapered to either twice or once a month depending on efficacy. Conjunctival hyperemia was cleared by the first month, while corneal inflammation resolved between 3 and 10 months. Adverse reactions were mostly mild, including stinging and redness.[86]

Topical calcineurin inhibitors

Topical cyclosporine

Cyclosporine is available in various concentrations including 0.05%, 0.09% and 0.1% with demonstrated efficacy in treating ocular rosacea, through its anti-inflammatory properties. Cyclosporine is typically used in adjunct with other therapies to treat more severe forms of ocular rosacea that exhibit marked ocular surface inflammation. Due to its anti-inflammatory properties, cyclosporine should not be recommended to patients with active ocular infections.[78]

In a double-blinded study, a 75% mean decrease in ocular manifestations including conjunctival hyperemia and blepharitis was observed in patients treated for 3 months with cyclosporine emulsion twice-daily.[87] Reported adverse reactions include irritation and stinging.[88]

Topical pimecrolimus and tacrolimus

Topical tacrolimus and pimecrolimus may be beneficial in treating eyelid manifestations associated with ocular rosacea, such as blepharitis.[89] Their efficacy is believed to be associated with their ability to downregulate local inflammation through inhibition of calcineurin.[90] Adverse reactions are typically mild and include burning and stinging, which can be mitigated by cooling before application.

Topical corticosteroids

0.1% dexamethasone phosphate, 0.1% flurometholone phosphate and 0.2% ioteprednol etabonate are corticosteroid ophthalmic solutions used in treating the more severe and recalcitrant cases of ocular surface inflammation in ocular rosacea. Due to their potent anti-inflammatory properties, corticosteroids should not be recommended to patients with active ocular infection.[91]

While corticosteroids are effective and potent in relieving ocular inflammation, long-term use is ill advised due to the high risk of rebound flares with discontinuation and increased intraocular pressure, potentially leading to the development of glaucoma, cataracts and local atrophy of the skin.[92] Thus, corticosteroids should only be used in conjunction with an ophthalmologist or optometrist, who can monitor intraocular pressure.

Topical metronidazole

Available in 1% cream, 1.0% gel formulations, metronidazole is an anti-inflammatory agent (antibiotic for anaerobic organisms only) typically applied on the face for treatment of cutaneous changes associated with rosacea. However, it has demonstrated efficacy for treating eye lid manifestations associated with ocular rosacea when applied to lid margins.

In a study where 10 patients applied metronidazole gel to the lid margin twice-daily in addition to practicing lid hygiene and warm compresses for 12 weeks, marked improvement was observed in rosacea associated blepharitis when compared to patients who only practiced lid hygiene and warm compresses. Adverse reactions include stinging and burning.[93]

Topical ivermectin

Available as a 1% cream, ivermectin has demonstrated efficacy in treating cutaneous rosacea via its anti-inflammatory properties and is especially effective in treating

rosacea with etiology related to D. folliculorum due to its antiparasitic properties. While typically used for cutaneous rosacea, ivermectin can also be used for treating cases of ocular rosacea with demodex infestation of the eyelashes.

In one trial involving 102 patients with demodex blepharitis, those who applied ivermectin 1% cream on the eyelashes for 15 min once-weekly for an average of 15 weeks achieved significant improvement in disease severity compared to control.[94] In another trial, 10 patients that applied ivermectin 1% cream to the eyelids noted significant improvement in blepharitis and conjunctival redness after 16 weeks.[95]

SYSTEMIC THERAPIES

Tetracyclines

Doxycycline

Doxycycline has a long history of use in treating ocular rosacea with several dosing options available, including a 40 mg modified release version intended for reducing the risk of gastrointestinal side effects. The efficacy of doxycycline is believed to be due to its anti-inflammatory properties instead of its antimicrobial effect. As such, doxycycline is usually prescribed in subantimicrobial doses (40–100 mg/day) to reduce risk of developing antibiotic resistance.[80,96] Typically, patients will start with 100 mg daily or BID for several months, and once the desired therapeutic effect is achieved, it is either discontinued or reduced to 40 mg daily.

In one study, patients treated with 100 mg doxycycline daily for 12 weeks showed marked improvements in several signs of ocular rosacea including Meibomian gland dysfunction, telangiectasias and erythema.[97] The effectiveness of 40 mg doxycycline was found to be equivalent with 100 mg doxycycline, and resulted in fewer adverse reactions (usually gastrointestinal).[98] In another trial, 15 patients treated with doxycycline 40 mg daily noted significant improvements in blepharitis and conjunctival redness after 12 weeks.[99]

Oxytetracycline

Oxytetracycline is another member of the tetracycline class of antibiotics with a similar mechanism of action with doxycycline and is also recommended in subantimicrobial doses (<500 mg/day) to limit gastrointestinal side effects. Oxytetracycline is functionally equivalent to tetracycline.

In a double-blinded trial, patients treated with 250 mg oxytetracycline twice-daily for 6 weeks showed higher rates of blepharitis and conjunctivitis clinical sign remission compared to placebo. Adverse effects were gastrointestinal, including nausea and sickness.[100] While oxytetracycline is an effective treatment option, doxycycline is often preferred due to its enhanced bioavailability, half-life and easier absorption, allowing for better patient adherence.[101]

Ondansetron

Ondansetron is a serotonin 5-HT3 receptor antagonist available as 4 mg tablets typically used in preventing nausea, but has some anecdotal evidence supporting its efficacy in treating ocular symptoms associated with rosacea. In the only case reported in the literature, a patient treated with 12 mg/day ondansetron showed marked ocular improvements by the fourth day.[102]

PROCEDURAL THERAPIES

Intense pulsed light (IPL)

IPL is a well-established treatment for facial rosacea, particularly in the treatment of telangiectasias and erythema through selective coagulation and ablation of blood vessels.[103,104] The procedure is performed using energy parameters suitable to the patient's Fitzpatrick skin type and comfort, with proper ocular protection. IPL is applied to the skin inferior and lateral to the lower eyelids followed by warm compress and manual expression of the Meibomian glands.

In one study, patients that received three or more IPL sessions achieved significant improvements in their dry eye disease symptoms, increase in oil flow and tear break-up time.[105] In another trial involving 17 patients with Meibomian gland dysfunction treated with four IPL sessions in 3-week intervals, improvements were observed in lower lid margin vascularity, meibum expression and ocular symptoms, but improvement were not maintained 6 months posttreatment.[106] In a recently conducted systematic review, Meibomian gland related dysfunction including tear breakup time, meibum quality and gland expressability were improved after treatment with IPL.[107]

Lipiflow

Lipiflow is a 12 min in-office procedure performed under topical anaesthesia which has been shown to be effective in the management of Meibomian gland disease. One

study showed that a single Lipiflow treatment was able to deliver a sustained mean improvement in Meibomian gland function and a mean reduction in dry eye symptoms over a 12-month period.[108] When compared to warm compresses, Lipiflow was found to be significantly more effective.[109] In a recently conducted systematic review and meta-analysis, Meibomian gland dysfunction measured by metrics including ocular surface disease index, standard patient evaluation of eye dryness, Meibomian glands yielding liquid secretion and Meibomian glands yielding secretion scores, were significantly improved after treatment with Lipiflow.[110]

CONCLUSION

Ocular rosacea is a chronic inflammatory condition currently affecting millions world-wide with a non-specific clinical presentation, hindering diagnosis and prompt treatment. While in most cases ocular rosacea coexists with the greater recognized cutaneous subtypes of rosacea, it is often overlooked or may precede the cutaneous manifestations. Combined with the complexity of diagnosis and the myriad similar differential diagnoses, ocular rosacea is undertreated, leaving patients with reduced quality of life and even vision loss in more severe cases. Although there are plenty of treatment options available, current therapies focus on symptom management, leaving patients to deal with cycles of remission and relapse. Newer modalities of treatment, such as Lipiflow and IPL have been found to be safe and effective for the treatment of Meibomian gland disease, the most common manifestation of ocular rosacea. Greater awareness and more effective therapies are required to relieve the burden of disease caused by ocular rosacea.

AUTHOR CONTRIBUTIONS

Ryan S. Q. Geng was involved in project conceptualization and writing of the original and editing stages of the manuscript. Jacqueline Slomovic was involved in writing of the original and editing stages of the manuscript. Adrienn N. Bourkas was involved in writing of the original manuscript. Allan Slomovic and Ronald G. Sibbald were involved in the editing stage of the manuscript and supervision.

CONFLICT OF INTEREST STATEMENT

A. S. has served as a consultant/advisor for Abbott, AiZtech, Alcon, Aqueous, Bausch Lomb, Labtician/Thea, Santen and Sun Pharma. A. S. owns equity in Abbott and Johnson & Johnson. R. G. S. has received honoraria from Perfuse, Quart Medical, Novartis, Medexus Pharmaceuticals Canada along with Ontario Gov't (Project ECHO Ontario Skin & Wound-Ministry of Health and Micro-credentials—through Ministry of Colleges and Universities and Sault College all unrelated to this workRSQG. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analysed during the current study.

ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication. Ethical Approval: not applicable.

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