BIELAK, Aleksandra, SPYCHALSKA, Maria, BOGIEL, Zofia, FORYŚ, Aleksandra, KAŁWAK, Monika, KUCZWALSKA, Daria, MACHAŁA, Antonina and TROCKA, Daria. Ocular Rosacea: Beyond the Skin. Quality in Sport. 2026;49:67332. eISSN 2450-3118.
https://doi.org/10.12775/QS.2026.49.67332
https://apcz.umk.pl/QS/article/view/67332

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 10.12.2025. Revised: 09.12.2025. Accepted: 27.12.2025. Published: 02.01.2026.

Ocular Rosacea: Beyond the Skin

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Abstract

Background: To the development of rosace contribute factors such as genetic, environmental, and neurovascular causes.. The ocular form affects an estimated prevalence of 10-46% of patients. Symptoms may include redness and tearing of the eyes, foreign body sensation, burning, dryness, itching, photophobia, blurred vision, eyelid margin telangiectasia, and periorbital erythema.

Purpose: Ocular rosacea is a long lasting condition that causes persistent inflammation of the eyes and eyelids. The aim of this paper is to organize information on the etiopathogenesis, diagnosis and treatment of this disease.

Methods: Comprehensive review of the literature available on PubMed, Google Scholar, Scopus database by searching the keywords “rosacea”, “ocular rosacea”, “ ocular rosacea treatment”, “keratitis”, “dry eye syndroms”

Results: Diagnosis requires vigilance because the disease is often confused with other ophthalmological conditions. There are no specific treatment guidelines for ocular rosacea. Managment options depend on the stage of the disease, ranging from conservative treatment based on proper eyelid hygiene and avoidance of triggers in the mildest cases to long-term systemic antibiotic therapy in patients with advanced disease.
Conclusions: Ocular rosacea is a disease that is not yet fully understood. Expanding research on this manifestation of rosacea is essential to develop standards for diagnosis and treatment. Collaboration between physicians from multiple specialties in patient care is essential to ensure rapid diagnosis and comprehensive treatment.

Keywords: doxycycline, dry eye disease, eye manifestations, keratitis, meibomian gland dysfunction, ocular rosacea, rosacea

I Introduction

Rosacea is a chronic, recurrent inflammatory dermatosis with a heterogeneous group of aetiological determinants. Typically affecting the central regions of the face, and characterised by a diverse array of clinical presentations. The disease is considered one of the most prevalent dermatological conditions, and its occurrence significantly impacts patients' quality of life and mental health [1]. Rosacea is a condition with a varied clinical framework, the course of which may include several various forms. The following forms can be distinguished in the classification: erythematotelangiectatic characterised by persistent erythema and the presence of teleangiectasia, papulopustular manifests itself as facial erythema with differing amounts of erythematous papules and pustules, phymatous is identifiable by significant thickening of the skin and hypertrophy of the sebaceous glands around the nose, concluding with the ocular subtype manifesting as conjunctivitis, blepharitis and chalazion [2]. Whilst individual forms may occur concurrently and overlap, each of them constitutes a distinct diagnostic and therapeutic entity. In the following paper, attention will be focused exclusively on ocular rosacea due to its specific characteristics, the possibility of potentially serious complications, and its growing clinical significance.

II Etiology

The factors contributing to the development of rosacea belong to a broad group, including genetic, environmental and neurovascular factors. Rosacea is characterised by a disorder of the innate immune system, in which the cathelicidin pathway plays a key role. Enhanced TLR2 expression is observed in patients with this disease, leading to overproduction of cathelicidin (LL-37) and pro-inflammatory mediators. CAMP expression is induced both through the vitamin D-dependent pathway and through independent mechanisms associated with endoplasmic reticulum stress. According to existing literature, genetic factors have an important role in the aetiology of rosacea. In addition, epidemiological studies demonstrate the disease does not occur equally across the population, a higher incidence has been observed in fair-skinned individuals, particularly those of northern European descent [3].

III Epidemiology

Rosacea is a condition that is most commonly diagnosed over the age of 25. The condition affects men and women equally. Women are diagnosed more often and earlier, presumably because women are more likely to report their symptoms to a doctor. The disease typically affects people with fair skin, but it also occurs in people with darker complexions. According to various sources, the ocular form accounts for between 10% and 46% of cases of rosacea and can occur independently of skin lesions. The prevalence of this condition may be higher in fair-skinned populations. Risk factors for all forms include genetic predisposition, obesity, nicotine use, diet and gender. The disease is particularly underestimated among older people and populations with darker skin tones, as erythema and telangiectasia are less visible in these groups, making diagnosis difficult. However, increased awareness in recent years has led to rosacea being diagnosed more frequently in these groups as well [2][3].

IV Symptoms

The National Expert Rosacea Committee classifies the ocular subtype based on the presence of symptoms such as watery or bloodshot eyes, foreign body sensation, burning or stinging, dryness, itching, and photophobia. Patients also report blurred vision, visible lid margin telangiectasia of the conjunctiva and eyelid margins, or the appearance of erythema of the eyelids and ocular region. Other sources indicate that this sub-type may manifest itself as a chalazion or hordeolum [4]. On the basis of the results of the German study, it can be concluded that ocular symptoms in patients with rosacea occur relatively frequently. Due to common

misdiagnosis, their presence may remain underestimated or inadequately documented [5]. The symptoms reported by patients may mimic other ophthalmological conditions. Therefore, it is important to conduct a detailed interview and thoroughly examine the patient from a dermatological perspective. Definitive confirmation can often be obtained on the basis of histological examination, as the descriptions of specific microscopic features described in the literature appear to be of lesser accuracy. The aforementioned symptoms present a considerable aesthetic challenge and substantially affect the quality of life of the patients.

V Diagnostics

According to the recommendations of the updated ROSacea COnsensus (ROSCO) panel, rosacea can be diagnosed if there is at least one so-called diagnostic symptom, i.e. persistent erythema in the central part of the face or hypertrophic skin lesions (phymatous lesions). In the absence of a primary symptom, a diagnosis may be considered in the presence of at least two so-called major symptoms, such as episodic redness (flushing), inflammatory papules and pustules, visible blood vessels (telangiectasia) or ocular symptoms (e.g. redness of the eyes, blepharitis). Additional symptoms, such as burning, skin burning, dryness or swelling, are helpful but are not sufficient for diagnosis on their own [4]. The complexity of ocular rosacea requires interdisciplinary collaboration between dermatologists and ophthalmologists. Coordination between both specialties enables a more accurate assessment of clinical manifestations and increases the probability of establishing an accurate and definitive diagnosis. Tear film parameters and fluorescein staining of the cornea are key indicators of eye disorders associated with rosacea. Reduced tear film break-up time and epithelial defects may indicate Meibomian gland dysfunction and tear film instability. It is important to assess the function of the Meibomian glands. The degree of obstruction or dysfunction may correlate with the severity of ocular symptoms and contribute to the development of dry eye and corneal epithelial damage. Decreased visual acuity is a recognised marker of severe corneal damage. This provides evidence that rosacea can lead to serious, potentially vision-threatening complications such as scarring, neovascularisation and corneal thinning [6][7].

VI Differential diagnosis

Differentiating ocular rosacea requires consideration of numerous conditions affecting the surface of the eye, eyelids, and cornea, which may present clinically similarly to the chronic

inflammation caused by this condition. It is crucial to distinguish the causes of chronic red eye from manifestations of ocular rosacea, such as non-inflammatory or infectious forms of blepharitis, primary Meibomian gland dysfunction, allergic and atopic conjunctivitis, aqueous-deficient dry eye (ADDE), and infectious diseases, including Herpes simplex keratitis. More advanced cases require a differential diagnosis with autoimmune diseases such as ocular cicatricial pemphigoid or cutaneous lupus erythematosus (LE) [8][9]. A comprehensive ophthalmological examination, including assessment of the eyelids, tear film and cornea, as well as correlation of ocular changes with the skin phenotype, allows ocular rosacea to be distinguished from clinically mimicking diseases and provides the basis for appropriate, targeted treatment.

VII Treatment

Currently, there are no official guidelines for managing ocular rosacea. Treatment regimens and progression to more advanced stages of the medication ladder depend on the clinical presentation and the experience of the treating physician. In this article, we present collected data on available strategies for ocular symptoms associated with rosacea.

Treatment of ocular rosacea depends on the severity of the disease. Referral to an ophthalmologist is recommended, as eye-threatening complications can occur during the course of the disease, including corneal ulcers, uveitis, scleritis, recurrent styes, and chalazia [10]. Referral to an ophthalmologist can be omitted if the disease is mild and basic treatment provides satisfactory symptom relief[11].

Treatment of mild-stage ocular rosacea

The mild form is characterized by symptoms such as dry eyes, mild itching, telangiectasia, and eyelid erythema[12].

Treatment of the grade one ocular rosacea is largely based on conservative approach. Maintaining proper lid-margin hygiene plays a significant role. Eyelids should be washed twice daily with a mild soap[13] – products intended for children can be used for this purpose. Warm compresses applied to the eyelid area can stimulate secretion in the Meibomian glands. For facial skin hygiene, it is recommended to avoid traditional soaps and replace them with solutions specifically designed for rosacea[4]. In cases of concomitant Demodex infection, there is data reporting effectiveness of a 50% tea tree oil [14].

It is also important to avoid factors that may worsen symptoms. The most common of these contributors is exposure to sunlight. Wearing sunglasses will reduce the indicators of photophobia, which often occur with severe dry eye [4]. Sunscreens should be used on the face [4]. Mineral products based on zinc oxide or titanium dioxide are best suited for this purpose, as they provide a physical barrier, not a chemical one, which can result in heat release as a byproduct [15]. Other factors that may aggravate the patient's condition include exposure to a warm climate, strong wind, stress, strenuous exercise, spicy foods, and alcohol consumption [16]. Avoiding medications that may worsen dry eye signs, such as antihistamines, hormone therapy, SSRI and SNRI antidepressants, and the popular cold remedies containing pseudoephedrine [17], is also an important contributor in supporting treatment.

According to recent studies, appropriate supplementation also appears to play a significant role in alleviating symptoms. Taking omega-3 fatty acids at doses of 325 mg of eicosapentaenoic acid (EPA) and 175 mg of docosahexaenoic acid (DHA) twice daily for three months led to significant improvement in dry eye signs in 65% of the studied patients [18]. Studies conducted on mice have shown that omega-3 fatty acid supplementation regulates inflammatory processes and angiogenesis, reducing symptoms typical of rosacea, such as flushing [19].

The primary medications used at this stage of treatment for this condition are lipid-based artificial tears, preferably preservative-free to prevent corneal irritation. These drops alleviate the manifestations of dry eye resulting from inflammation and stabilize the tear film [20][21].

Treatment of intermediate-stage ocular rosacea

Stage two is characterized by symptoms such as a burning sensation, swelling, and redness of the eyelids, as well as a chalazion resulting from blocked and inflamed Meibomian glands [12]. In addition to the conservative treatment described above, topical anti-inflammatory medications are used in this stage to prevent potential complications.

The most promising drug at the moment is topical cyclosporine eye drops. Cyclosporine, typically applied twice daily at a concentration of 0.05-0.1%, effectively reduces inflammation by inhibiting the T-cell-modulated cellular response, improves tear production, and reduces symptom severity. It is a good alternative to steroids due to its broad anti-inflammatory effects and lack of steroid-related complications [22][23]. In one study, topical cyclosporine demonstrated better results in improving ocular manifestations, eye health, and tear film quality than oral doxycycline, commonly used for more severe forms of ocular rosacea [22]. Topical tacrolimus at a concentration of 0.03% has a similar effect [22].

Azithromycin drops, at a concentration of 1-1.5%, are used during flare-ups. Two dosing regimens are available: twice daily for two days or once daily for 5 days. The antibiotic reduces inflammation and improves tear film quality [24].

Other substances used in the treatment of ocular rosacea include Lifitegrast 5%, an immunomodulatory drug that alleviates dry eye symptoms. When used twice daily, it reduces dryness and corneal staining [4]; Brimonidine, used in the treatment of glaucoma, to reduce corneal redness [25]; and topical preparations (eye drops or ointments) containing a silver complex with metronidazole [26]. For signs of blepharitis, such as swelling and erythema, topical pimecrolimus ointments with or without metronidazole are effective [27]. Erythromycin and metronidazole eye drops have also been shown to be effective [28]. A 1% ivermectin cream is often used for blepharitis and conjunctival erythema. Due to its antibacterial and antiparasitic effects, it is particularly effective in cases of concomitant Demodex infection [29][30].

Steroid-containing eye drops effectively reduce superficial corneal inflammation, but due to their side effects – steroid-induced glaucoma, hypertension, cataracts – they should be reserved only for cases that do not respond to immunomodulatory treatment [4].

Treatment of severe-stage ocular rosacea

In the most severe, advanced stage of ocular rosacea, blurred vision, sensitivity to light, corneal inflammation, acute eyelid inflammation, eyelash loss, and intense conjunctivitis occur [12]. This form requires systemic treatment to suppress the inflammatory reaction. The most commonly used drugs are antibiotics from the tetracycline group. In addition to their antibacterial effects, those antibiotics may have a positive effect on changes in interleukin and nitric oxide levels, B cell activation, and collagen abnormalities, which are responsible for the abnormalities in the ocular manifestations of the disease [31].

The first-line therapy of choice is oral doxycycline. It has anti-inflammatory and antiangiogenic effects and fewer side effects than first-generation tetracyclines [21]. There are no official recommendations regarding dosage or duration of therapy. The most commonly prescribed dose is 40 mg daily, usually for 12 weeks. In more severe cases, the amount can be increased to 100 mg once or twice daily for several weeks and then reduced to a maintenance dose of 40 mg daily [20][32]. Many patients may experience a flare up after discontinuing the drug, so long-term sustaining therapy may be necessary in some cases [21]. Doxycycline at a dosage of less than 50 mg has anti-inflammatory properties but no antibacterial activity, and the incidence of gastrointestinal side effects is significantly reduced; therefore, a maintenance dose of 40 mg

is safe for long-term use. No development of resistance to this antibiotic has been demonstrated despite the use of suboptimal amounts [33]. Recent studies indicate that azithromycin eye drops are as effective in relieving inflammatory symptoms in ocular rosacea as oral doxycycline, with fewer side effects [34][35]. However, these reports have not yet been confirmed, and oral doxycycline remains the first-line treatment for severe ocular rosacea.

An alternative to doxycycline is myocycline at a dose of 100 mg once daily for 12 weeks [24]. In patients with tetracycline intolerance, azithromycin [36] and erythromycin[37] are alternatives. In acute cases that do not respond to antibiotics, oral cyclosporine[24] is used.

Some sources state that for systemic therapy to be effective for ocular symptoms, treatment should be continued for 3 to 6 months [27], but there are no established protocols or expert consensus on this issue.

Oral antibiotic therapy has been proven to significantly improve tear production, alleviate ocular surface lesions, and alleviate patient symptoms. However, it does not always improve vision or eliminate corneal inflammation. It should be used with caution due to numerous side effects, particularly those associated with prolonged therapy [31].

Other Therapy Methods

Intense Pulsed Light Therapy

IPL is a technology widely used in dermatology, based on the emission of high-energy broadband light pulses that penetrate the skin and affect light-absorbing structures. In the case of ocular rosacea, light is absorbed by dilated blood vessels, inducing coagulation, free radical damage to the blood vessels, and subsequent vessel healing [38]. A positive impact on the function of the Meibomian glands has also been reported, based on the thermal effect and resulting increase in secretion and improvement in drainage from the Meibomian glands. Improving these parameters limits bacterial growth, which reduces inflammation [39]. Studies [40][41][42] have shown significant improvements in dry eye symptoms and parameters such as tear film break-up time and tear film stability. Additionally, the results are promising despite the lack of direct IPL exposure to the eyelids – eyelid shields are used during the treatment, so only the lower eyelid margins are exposed to the light. This effect may be due to the beneficial effect of IPL on increasing the concentration of anti-inflammatory mediators and antioxidants [40].

Surgical Treatment

Surgical treatment for rosacea is rarely used and is necessary in cases where chronic inflammation leads to complications that do not respond to standard treatment [12]. In complicated ocular rosacea, complications may include recurrent, multiple chalazions, which, if unresponsive to conservative treatment, require incision and curettage [43], as well as scarring of the eyelids (e.g., entropion or ectropion), which require reconstructive treatment [21]. More serious changes that directly impact visual acuity include corneal ulcers and the resulting perforations, as well as corneal scarring caused by inflammation. Corneal perforation is an indication for immediate surgical intervention – possible methods of treatment include tissue glue, lamellar keratoplasty, and penetrating keratoplasty [43]. Due to the pathogenesis of ocular rosacea, where corneal disorders are often accompanied by corneal neovascularization and recurrent inflammation, patients with this condition are poor candidates for full-thickness keratoplasty, hence lamellar keratoplasty is more effective [24]. In the case of corneal scarring, scleral contact lenses may also improve the quality of vision [24].

New perspectives

Recent studies have shown that patients with ocular rosacea have increased activity of MAPK kinases (primarily ERK1/2 and p38) in ocular tissue and increased activity of the NF-κB pathway in eyelid biopsies. These mechanisms may lead to the development of new targeted therapies [44].

VIII Discussion and conclusions

Ocular rosacea is a long lasting condition characterized by periods of flare ups and remission. It can greatly affect the patient's quality of life and demands careful management through diet, change of lifestyle, and medication. The greatest challenge we face in clinical practice when dealing with this condition is our lack of knowledge. The underlying causes of rosacea are not yet fully understood, and ocular rosacea is one of the rarest and least studied forms of the disease. The disease can have many manifestations and a wide spectrum of symptoms, making it difficult to indentify. The lack of appropriate diagnostic tools and algorithms often leads to missed or incorrect diagnoses. Approximately 20% of patients develop ocular symptoms before the appearance of classic skin symptoms [45] and some of these patients never develop skin signs, making it even more difficult to come to accurate findings. The disease is often misdiagnosed as dry eye syndrome, chronic blepharitis, or bacterial infections [4]. However, a correct diagnosis does not guarantee appropriate treatment. Guidelines for the managment of

ocular rosacea are broad, and there are no specific studies that would provide an effective treatment protocol. In many patients, the proposed treatment provides only partial improvement, therefore, an individualized therapy regimen is necessary, based on the stage of disease progression and the patient's needs. Data provided in the recommendations are based primarily on clinical practice, not randomized trials. In addition, many experimental therapies with potentially beneficial effects have been developed for the treatment of ocular rosacea, but have not been confirmed in independent studies.

To improve the quality of care for patients with ocular rosacea, clear diagnostic criteria are needed to reduce the rate of misdiagnosis. The literature also lacks a sufficient number of randomized trials specifically focusing on ocular rosacea. More detailed research on the topic would enable the development of specific guidelines, establish a "gold standard" for the treatment of ocular rosacea, and eliminate approaches that are not effective. In the future, we hope to see the development of specialized targeted therapies based on an understanding of the disease's pathogenesis and mechanisms behind it. Collaboration between different specialists—primary care physicians, dermatologists, and ophthalmologists—is essential for early diagnosis, proper treatment, and the preventing complications.

It's important to understand that ocular rosacea isn't a secondary condition resulting from skin disease—it's a standalone condition affecting the eye surface, with its specific immune, vascular, and microbiological abnormalities. Gaining a better understanding of this condition and developing treatment strategies will allow for improved patient care, more effective symptom control, and improved quality of life.

All authors have read and agreed with the published version of the manuscript.

Disclosure:

No disclosures.

Funding statement:

This research did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable

Data availability statement

Not applicable.

Conflict of Interests Statement

The authors declare no conflict of interest.

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