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Ocular Rosacea: An Updated Review

Karim Mohamed-Noriega, MD, Denise Loya-Garcia, MD, PhD,† Guillermo Raul Vera-Duarte, MD,† Fernando Morales-Wong, MD,* Gustavo Ortiz-Morales, MD,† Alejandro Navas, MD, PhD,† Enrique O. Graue-Hernandez, MD, MSc,† and Arturo Ramirez-Miranda, MD, PhD†*

Purpose: Ocular rosacea is a chronic inflammatory disorder affecting the ocular surface, often associated with cutaneous rosacea. This review aims to explore its pathogenesis, treatment approaches, and future directions for management.

Methods: A review of current literature on the pathophysiology, clinical features, and treatment strategies of ocular rosacea in adults and children (pediatric blepharokeratoconjunctivitis) was conducted. Emerging research on immune dysregulation, microbiome alterations, and potential therapeutic targets was analyzed.

Results: Ocular rosacea involves dysregulation of the immune and neurovascular systems, with toll-like receptor activation and complement system involvement leading to chronic ocular surface inflammation. Alterations in the ocular microbiome have been implicated in disease progression. Treatment strategies emphasize a stepwise approach, incorporating ocular and skin hygiene, lifestyle modifications, and pharmacological interventions. Recent advancements in understanding the disease mechanisms have led to the exploration of targeted therapies, including biologics and small-molecule inhibitors.

Conclusions: Ocular rosacea remains challenging to diagnose and treat, particularly in children (pediatric blepharokeratoconjunctivitis), often leading to delayed intervention and poor outcomes. A multidisciplinary approach, including new therapeutic options, holds promise for improving patient care. Further research into the genetic and molecular basis of ocular rosacea may enable more personalized treatments.

Key Words: ocular rosacea, keratitis, blepharokeratoconjunctivitis (PBKC), dry eye disease, meibomian gland dysfunction

(*Cornea* 2025;44:525–537)

Rosacea is a multifactorial, chronic inflammatory skin disease involving the pilosebaceous units of the central facial skin (cheeks, chin, nose, and central forehead).[1,2] It is a chronic condition involving dysregulation of the innate immune and neurovascular systems characterized by facial redness, visible blood vessels, flushing, sensitive skin, and ocular discomfort. Clinical manifestations include erythema, telangiectasias, papules, pustules, fibrosis, and ocular manifestations. The term rosacea is derived from the Latin word *rosaceous (rosy)*, describing the frequent facial and nasal redness occurring in rosacea.[3]

Ocular rosacea is characterized by inflammation of the ocular surface tissues, including the eyelid margin (blepharitis) and the tear film (manifesting as instability, eye irritation, red eyes, dryness, and conjunctivitis, among other symptoms).[4,5] Chronic ocular involvement can lead to corneal neovascularization and keratitis, potentially resulting in corneal scarring and perforation. The severity of ocular symptoms does not always correlate with that of skin symptoms.[6] Rosacea also has been associated with emotional distress, low self-esteem, and the avoidance of social situations.[7]

Various topical and systemic treatment options are available for rosacea, each with varying degrees of efficacy across different phenotypes. Considering the psychosocial impact that the clinical features of rosacea can have on patients, it is crucial to identify treatments that effectively alleviate these symptoms. The objective of this review is to analyze existing literature, clinical trials, and current treatment options of ocular rosacea.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Ocular rosacea, classified as subtype IV, is defined by the National Rosacea Expert Committee as the presence of 1

Received for publication October 4, 2024; revision received November 18, 2024; accepted November 19, 2024. Published online ahead of print January 14, 2025.

From the *Department of Ophthalmology, University Hospital and Faculty of Medicine, Autonomous University of Nuevo León (UANL), Monterrey, Nuevo Leon, Mexico; and †Instituto de Oftalmologia Fundacion Conde de Valenciana IAP, Mexico City, Mexico.

The authors have no funding or conflicts of interests to disclose.

Conceptualization (K. Mohamed-Noriega, G. R. Raul Vera-Duarte, G. Ortiz-Morales, A. Ramirez-Miranda); Investigation (K. Mohamed-Noriega, G. Ortiz-Morales, G. R. Raul Vera-Duarte, F. Morales-Wong); Methodology (G. R. Raul Vera-Duarte, G. Ortiz-Morales); Project administration (A. Ramirez-Miranda, E. Graue-Hernandez, A. Navas, K. Mohamed-Noriega); Supervision (A. Ramirez-Miranda, E. Graue-Hernandez, AN, K. Mohamed-Noriega); Validation (K. Mohamed-Noriega, E. Graue-Hernandez, A. Navas, A. Ramirez-Miranda); Visualization (G. R. Raul Vera-Duarte, K. Mohamed-Noriega, F. Morales-Wong); Roles/Writing—original draft (G. Ortiz-Morales, G. R. Raul Vera-Duarte); and Writing—review & editing (K. Mohamed-Noriega, G. Ortiz-Morales, G. R. Raul Vera-Duarte, F. Morales-Wong, A. Ramirez-Miranda).

Correspondence: Arturo Ramirez-Miranda, MD, PhD, Instituto de Oftalmologia Fundacion Conde de Valenciana IAP, Chimalpopoca 14, Centro, Cuauhtémoc, 06800 Ciudad de México, CDMX. CP 06800 Mexico (e-mail: arturorammir@gmail.com).

or more of the following signs or symptoms: watery or bloodshot appearance, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, conjunctival and eyelid margin telangiectasias, or eyelid and periocular erythema.[1,8] Additional signs include blepharitis, conjunctivitis, and irregular eyelid margins; chalazia and styes are also frequent indicators (Figs. 1, 2). Nonetheless, rosacea is primarily diagnosed clinically and lacks specific diagnostic criteria (Table 1).

Ocular rosacea can present with many symptoms, including redness, burning, stinging, foreign body sensation, photophobia, and blurred vision. Clinical signs may encompass conjunctivitis, blepharitis, meibomian gland dysfunction, and corneal involvement (Figs. 1 and 2).[9] A thorough history taking and clinical examination are essential to diagnose ocular rosacea. Although some textbooks consider the microscopic signs of rosacea as nondiagnostic, experienced dermatopathologists can typically make the diagnosis through careful histological evaluation. Accurate diagnosis is crucial as ocular rosacea may not respond as expected to topical therapy and can lead to severe corneal involvement with corneal scarring, neovascularization, thinning, and even corneal perforation if left untreated (Fig. 3).

Clinicians must be aware of potential differential diagnoses as ocular rosacea can be mistaken for dry eye, blepharitis, conjunctivitis, or keratitis. Considering the patient's history, including any symptoms suggestive of rosacea, and examining the central face for skin changes and rhinophyma can aid in making the correct diagnosis (Figs. 1, 3).

Studies emphasize the importance of considering ocular rosacea as a potential cause of persistent eye redness and relapsing conjunctivitis-blepharitis, particularly in elderly patients. The association between cutaneous rosacea and ocular rosacea can vary, with facial changes as the primary feature in 53% of cases, concurrent skin and ocular changes in 27%, and ocular changes as the primary feature in up to 20% of cases.[10] The severity of ocular symptoms may not correlate with the severity of cutaneous findings, in which symptoms may show periods of exacerbation or remission; however, the disease usually progresses over time.[11,12]

The 2019 Global ROSacea COnsensus (ROSCO) panel guidelines advocate a comprehensive diagnostic approach for ocular rosacea, encompassing slit-lamp examination, eyelid and meibomian gland assessment, tear film evaluation, and corneal examination.[13] Although ocular symptoms may be nonspecific and subtypes can overlap, a thorough history taking and physical examination are crucial for timely disease recognition and management. Furthermore, recognizing dermatological findings of rosacea in patients with darker skin may be more challenging.

ROSCO provides essential insights into the features and severity assessment of ocular rosacea[13] and describes various ocular rosacea features, including lid margin telangiectasia, blepharitis, keratitis, conjunctivitis, and anterior uveitis.[14] The consensus also outlines considerations for assessing the severity of these ocular rosacea features. For lid margin telangiectasia, considerations include the degree of vascularization, density, meibomian gland dysfunction, and the presence of evaporative tear dysfunction. In the case of blepharitis, factors such as the degree of eyelid inflammation, pain, and swelling are essential. For keratitis, the assessment includes the location and degree of inflammation, defects in staining (eg, ulceration), foreign body

TABLE 1. Classification of Ocular Rosacea

Category	Ocular Manifestations
Diagnostic criterion	
Persistent centrofacial erythema	May manifest as erythema on the eyelid margins
Phymatous changes	Not directly associated with ocular manifestations
Major criterion	
Papules and pustules	Not directly associated with ocular manifestations
Flushing	May exacerbate ocular redness
Telangiectasia	Telangiectasias on the eyelid margin, especially in the interpalpebral area
Ocular manifestation	
Eyelid margin telangiectasias	Presence of telangiectasias on the eyelid margins, particularly in the interpalpebral area
Interpalpebral conjunctival injection	Conjunctival redness between the eyelids, characteristic of ocular rosacea
Spade-shaped corneal infiltrates	Corneal spade-shaped infiltrates, which may lead to more severe complications
Scleritis and sclerokeratitis	Severe inflammation of the sclera and cornea
Secondary criterion	
Burning sensation	Ocular burning, not specific to rosacea but common in many patients
Stinging sensation	Similar to burning, this sensation may occur with or without visible inflammation
Edema	May accompany severe ocular inflammation
Dry appearance	The skin around the eyes may appear dry, associated with meibomian gland dysfunction and blepharitis
Evaporative tear dysfunction	Reduced tear breakup time, leading to ocular dryness
Other common signs	
Chalazion	Obstruction and inflammation of the meibomian glands, characteristic of ocular rosacea
Posterior blepharitis	Inflammation of the eyelids with meibomian gland dysfunction
Corneal infiltrates	May progress to corneal ulceration if not properly treated

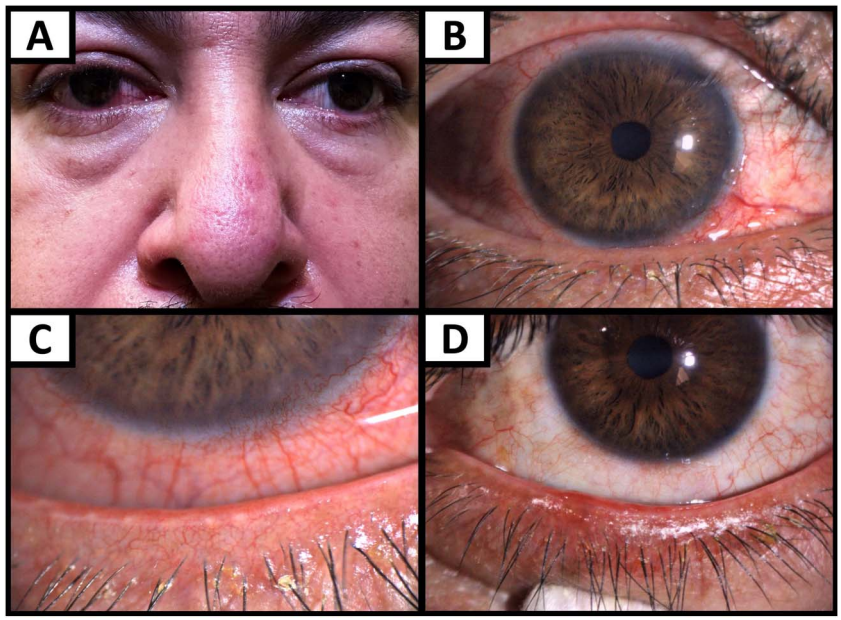

FIGURE 1. Representative images of a male patient with ocular rosacea. A, Bilateral asymmetric recurrent and chronic red eye. The face has classic signs of rhinophyma, skin papules, telangiectasias, flushing, and hyperemia. B and C, Right eye with marked hyperemia and localized ciliary injection; discrete peripheral marginal infiltrates; chronic meibomian gland dysfunction with eyelid margin hyperemia, telangiectasias, meibomian gland clogging, and thickened meibum; and anterior blepharitis with eyelash scales. D, Left eye shows a mild red eye and signs of a partially healed hordeolum at his inferior eyelid border.

sensation, and pain. Conjunctivitis severity is evaluated based on interpalpebral congestion, the degree of conjunctival injection, and foreign body sensation. Anterior chamber cell count and flare assess anterior uveitis. These considerations are recommendations rather than a consensus due to the limited number of ophthalmologists involved, both of whom either agreed or strongly agreed with the descriptions.[15,16]

This Global ROSacea COnsensus panel advocates for a phenotype-based approach to diagnosing and managing rosacea, allowing for more individualized care based on the clinical features presented by the patient. Clinical tools such as the "Rosacea Tracker" have been developed to help physicians monitor changes in rosacea phenotypes, patient impact, and treatment response.[13] These tools facilitate the implementation of the phenotype approach in daily clinical practice. Incorporating these insights provides a more comprehensive understanding of ocular rosacea, emphasizing the need for precise diagnosis and a thorough evaluation of symptoms and clinical signs. Including specific considerations for each feature aids in standardizing severity assessment and guiding appropriate clinical management. This approach addresses the clinical aspects of ocular rosacea and considers its impact on the patient's quality of life, thereby promoting a holistic and patient-centered care strategy.

Ocular rosacea presents a diagnostic challenge due to its overlapping symptoms with other inflammatory and infectious ocular conditions. Key differential diagnoses include blepharitis, conjunctivitis, meibomian gland dysfunction, and conditions such as dry eye syndrome, which share symptoms of eye redness, irritation, and discomfort.[9] Distinguishing ocular rosacea from these conditions requires attention to specific indicators such as meibomian gland dysfunction, hyperemia, telangiectasia of the eyelid margins, and chronic inflammation. In addition, allergies, episcleritis, and certain systemic conditions with ocular manifestations, such as lupus and Sjögren syndrome, should be considered, particularly in cases where symptoms are refractory to initial treatments.[17] Accurate diagnosis often relies on a collaborative approach between dermatologists and ophthalmologists, particularly given the condition's tendency to mimic dermatological and ophthalmological symptoms.[18]

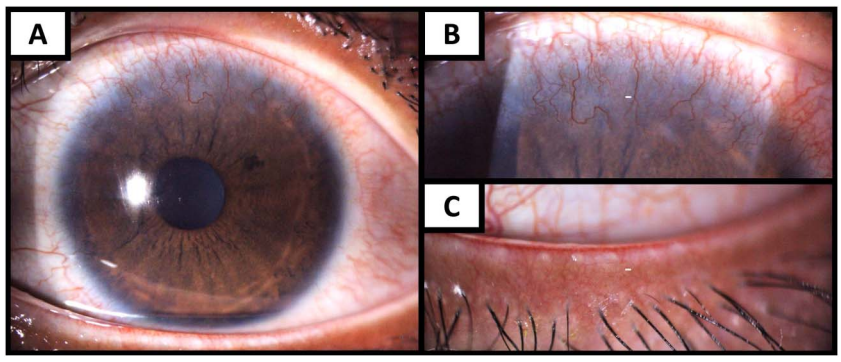

FIGURE 2. Ocular manifestations of rosacea. A, Chronic red eye in ocular rosacea. Recurrent asymmetric red eye. B, After careful exploration of the superior corneal pannus with localized ciliary injection, discrete peripheral marginal infiltrates are observed. C, In addition to chronic posterior blepharitis with eyelid margin hyperemia, telangiectasias, meibomian gland clogging, and thickened meibum are observed.

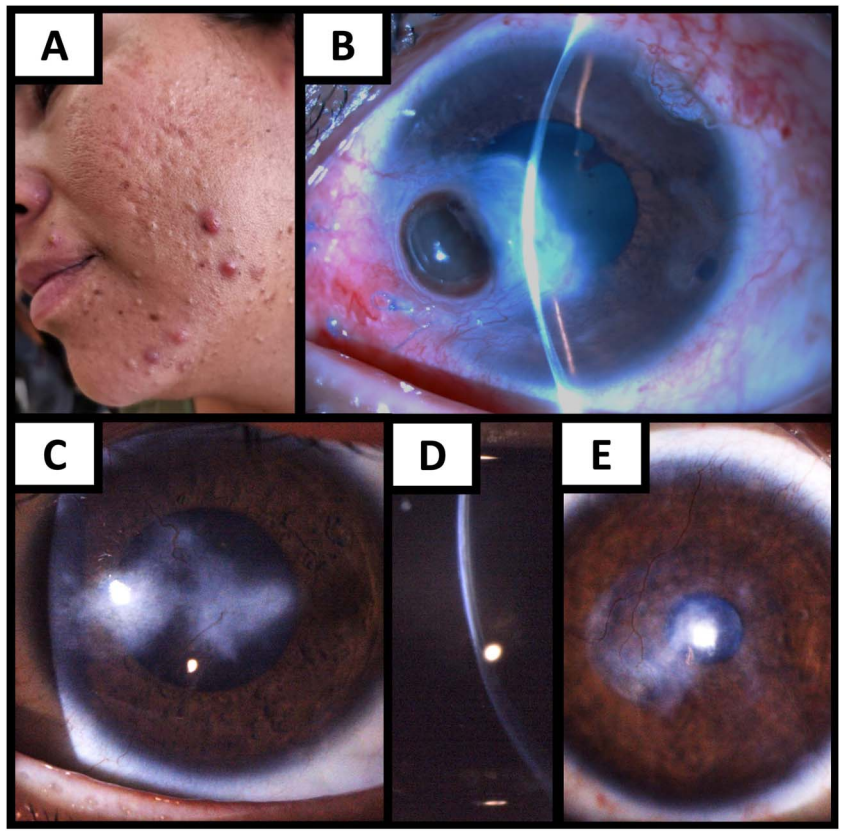

FIGURE 3. Corneal involvement in ocular rosacea. A, Facial characteristics of rosacea with skin papules, pustules, hyperemia, telangiectasia, and rhinophyma. B, Peripheral corneal perforation sealed with uvea. The cornea has extensive scarring and neovascularization. Other areas of the cornea show peripheral marginal and phlyctenular corneal scars with neovessels. Remnants of a failed conjunctival graft are observed. C, D, and E, Bilateral neovascularized corneal scar involving the anterior and central stroma.

EPIDEMIOLOGY

Rosacea is an underdiagnosed disorder, with evidence suggesting a susceptibility toward disease progression and a global prevalence of approximately 5.5%.[19,20] The onset age of rosacea typically ranges from 25 to 55 years, occurring equally frequently in men and women. However, women are more commonly diagnosed with rosacea and tend to be diagnosed earlier. A possible explanation for this disparity is that women may seek medical care more often and earlier than men. It is more commonly observed in individuals with fair skin, specifically those classified as Fitzpatrick skin types I–II.[21] However, it can also affect individuals with brown or darker skin tones. Ocular rosacea comprises between 10% and 50% of all cases of cutaneous rosacea[4,22,23] and can occur even without skin manifestations.

In certain populations, the prevalence of rosacea can reach up to 22%, with the ocular subtype accounting for up to 50% or more of cases.[5,24] These data can vary based on the diagnostic criteria used and the population assessed. Risk factors of all subtypes of rosacea include genetics, obesity, smoking, diet, and biological sex.[24,25] Pediatric cases of ocular rosacea have been reported and it should be considered in the evaluation of pediatric patients with inflammatory eye conditions, although it is one of the most common causes of childhood blepharoconjunctivitis.[26–29]

The prevalence of ocular rosacea may be underestimated as it is frequently underdiagnosed, particularly among the elderly and within certain population groups. However, in recent years, the disease has become increasingly recognized in populations with darker skin tones. It is generally underdiagnosed in these demographics because erythema and telangiectatic changes are less pronounced, often requiring the presence of papulopustular or phymatous changes to be readily detectable.[23]

PATHOPHYSIOLOGY

Overview of Ocular Rosacea Pathophysiology

Ocular rosacea is a chronic and debilitating condition that affects the ocular surface and surrounding structures.[30] The precise etiology of rosacea, including the ocular variant, is still unknown; however, it is believed to involve a complex interplay of abnormalities in the innate and adaptive immune systems, mast cell dysfunction, and neurovascular regulation.[23,31] Molecular and cellular markers have been identified despite the idiopathic nature of ocular rosacea. Genetic predisposition, environmental factors, microbial impacts, and immune system anomalies influence the development and advancement of rosacea. These abnormalities are believed to underlie the various symptoms of the disease.

Ocular rosacea is believed to have similar underlying mechanisms to cutaneous rosacea, including innate immunity, inflammation, vascular dysfunction, and neurosensory abnormalities.[32] Considering that rosacea entails activating the skin's immunological and neurological systems in reaction to physical, chemical, or biological cues, the alterations caused

by gut dysbiosis could contribute to the advancement of the illness, heightened severity, flare-ups, or permanent symptoms.[33] The chronic nature of ocular rosacea and the potential for sight-threatening complications underscore the importance of understanding its underlying pathogenesis. Emerging evidence suggests that ocular and facial microbiome alterations may be crucial in the development and perpetuation of ocular rosacea.[30]

Immune System Involvement, Inflammatory Mechanisms, and the Role of Cytokines and Chemokines

Ocular rosacea is characterized by immune system dysfunction. Rosacea seems to cause an excessive activation of the innate immune system, specifically toll-like receptors (TLRs) and the complement system.[30] The excessive stimulation of this process results in an elevated production of proinflammatory cytokines and chemokines, which in turn contributes to the development of the ocular symptoms associated with the condition. T cells, a component of the adaptive immune system, contribute to the inflammatory response seen in ocular rosacea.[34] In addition to the immune system, vascular and neurosensory abnormalities have also been implicated in the pathogenesis of ocular rosacea. Emerging research suggests that oxidative stress and the generation of reactive oxygen species also may contribute to the development and progression of ocular rosacea.[22,35] Increased oxidative stress can lead to cellular damage, inflammation, and vascular dysfunction, all hallmarks of ocular rosacea.[36]

Ocular rosacea is further distinguished by vascular impairment and changes in neurosensory function. Ocular rosacea often presents with common manifestations such as increased vasodilation, telangiectasia, and vascular hyperreactivity.[37] These vascular changes can increase permeability, edema, and ocular surface inflammation. In addition to vascular dysfunction, neurosensory abnormalities have also been reported. Patients with ocular rosacea often experience ocular discomfort, irritation, and photosensitivity, suggesting the involvement of the ocular sensory nerves.[38] The precise mechanisms underlying these neurosensory modifications must be better comprehended; however, they may involve neurogenic inflammation and altered pain perception.

The pathogenesis of ocular rosacea involves a complex interplay between the innate and adaptive immune systems, resulting in chronic ocular surface inflammation.[39] Patients with ocular rosacea exhibit increased production of proinflammatory cytokines; chemokines; and other mediators such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs).[34,40] Hormones also play a role in regulating inflammation and maintaining homeostasis. Androgenic hormones, such as testosterone, have been shown to influence the inflammatory response and function of the meibomian glands, which are often affected in ocular rosacea.[41] In addition, the potential involvement of estrogen and its receptors in regulating inflammation and vascular function on the ocular surface has been explored[42] as gender differences in the prevalence and severity of rosacea have been observed.

Furthermore, the corneal epithelium expresses soluble vascular endothelial growth factor (VEGF) receptor-1 and membrane-expressed VEGF receptor-3, sequestering angiogenic factors such as VEGF-A and VEGF-C, respectively.[43–45] This process limits angiogenesis and potentially restricts inflammatory cell infiltration following ocular stress. Peripheral immunoregulatory mechanisms, such as programmed death ligand-1, also protect ocular tissues from T-cell–mediated damage, seen in conditions such as dry eye disease and with corneal transplants.[45,46] The loss of homeostasis between the antiinflammatory and proinflammatory factors contributes to the vasodilation, vascular hyperreactivity, and disruption of the ocular surface integrity observed in ocular rosacea. In addition, activating pattern recognition receptors, such as TLRs, on ocular surface cells can trigger and perpetuate the inflammatory cascade in this condition.[34,47] Ultimately, the stimulation of TLRs leads to the activation of nuclear factor kappa B (NF-κB) through all known pathways.[48]

Koebnerisin is an antimicrobial peptide involved in immune-mediated inflammatory responses across various dermatological conditions, including psoriasis and rosacea.[34,49,50] Regulated by TH1 and TH17 cells, koebnerisin acts as a leukocyte chemoattractant. Studies have shown high levels of koebnerisin in skin biopsies from patients with rosacea. In vitro experiments indicate that human keratinocytes cultured with koebnerisin secrete MMP-9 and VEGF, suggesting a proangiogenic role. In addition, koebnerisin induces the production of proinflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-1β in keratinocytes and macrophages, further propagating the inflammatory response.

Cytokines and chemokines play a crucial role in the pathogenesis of ocular rosacea. Elevated levels of proinflammatory cytokines, including IL-1β, TNF-α, and IL-6, have been observed in the tears and conjunctival tissues of patients with this condition.[15,34,51] These inflammatory mediators can induce vascular changes, activate and recruit immune cells, and compromise the integrity of the ocular surface. In addition, chemokines such as IL-8, monocyte chemoattractant protein-1, and growth-regulated oncogene-α contribute to the recruitment and activation of neutrophils, monocytes, and other inflammatory cells to the ocular surface, further exacerbating the inflammatory response.[16,34,48] The dysregulation of cytokine and chemokine networks in ocular rosacea can lead to chronic inflammation, tissue damage, and the development of secondary complications, including meibomian gland dysfunction, corneal scarring, and vision impairment. In rosacea, elevated levels of cathelicidins, antimicrobial peptides, are present in the epidermis. These cathelicidins undergo aberrant processing, resulting in forms that can promote both proinflammatory and proangiogenic activities.[52,53] These inflammatory mediators also play a role in perpetuating the inflammatory cycle as they can stimulate the production of additional cytokines and chemokines and create a self-sustaining inflammatory process. Understanding the interplay of these inflammatory factors is crucial for the development of effective treatment strategies for ocular rosacea.

Microbial Factors

The complex nature of ocular rosacea, with its interplay of immune, vascular, and neurosensory factors, underscores the need for a comprehensive approach to understanding and managing this condition as it presents a challenge in clinical practice. Recent studies have highlighted the potential significance of the ocular microbiome in the pathogenesis of ocular rosacea. Mounting evidence suggests that alterations in the normal ocular microbial flora may contribute to the development and perpetuation of this condition.[38] Specifically, changes in the diversity and composition of the ocular microbiome have been observed in patients with ocular rosacea. These microbial imbalances may lead to increased inflammation, disruption of the ocular surface, and impaired immune responses, all of which can contribute to the clinical manifestations of ocular rosacea.[54] The precise mechanisms by which the ocular microbiome influences the development of ocular rosacea are not fully understood, but it is hypothesized that the dysbiosis of the ocular microbiome can trigger or exacerbate the underlying immune-mediated and vascular processes that characterize the disease. This emerging area of research underscores the need for further investigation into the role of the ocular microbiome in the pathogenesis of ocular rosacea as it may provide new insights into the diagnosis, treatment, and prevention of this condition. Demodex mites have also been implicated in the pathogenesis of ocular rosacea as their presence and proliferation on the ocular surface may contribute to the inflammatory response and ocular surface damage observed in this disease.[54,55] Bacteria and other pathogens such as *Bacillus oleronius* in the hindgut of Demodex mites may also play a role in the development of ocular rosacea by inducing an inflammatory response and disrupting the integrity of the ocular surface.[56,57] Factors that can alter the ocular surface microbiome, such as dry eye syndrome, contact lens wear, and antibiotic use, may contribute to the development or exacerbation of ocular rosacea.[57]

Genetic Predisposition

The genetic basis of ocular rosacea remains uncertain, but emerging evidence suggests that genetic factors play a role in the development of and susceptibility to this condition. Specific genetic variations and polymorphisms, including those involved in immune regulation, vascular function, and inflammatory pathways, have been associated with an increased risk of rosacea.[30] Genetic factors are estimated to account for approximately half of the pathogenic mechanisms in rosacea while environmental factors contribute to the other half.[58] The increased correlation of rosacea in homozygous twins compared with heterozygous twins highlights the hereditary component of the condition.[30,59] Multiple genes have been implicated in the development of rosacea, with genome-wide association studies identifying single-nucleotide polymorphisms and human leukocyte antigen (HLA) associations involving HLA-DRA, BTNLA2, HLA-DRB103:01, HLA-DQB102:01, and HLA-DQA105:01.[60] Interestingly, these HLAs are also associated with other autoimmune illnesses, providing additional evidence for the involvement of the immune system in the development of rosacea. Nevertheless, the specific genetic underpinnings of ocular rosacea remain an active area of research, and more studies are needed to fully elucidate the genetic and genomic factors contributing to this condition. Genetic factors may contribute to individual differences in the clinical presentation and severity of ocular rosacea. Understanding the genetic basis of ocular rosacea may lead to the development of personalized treatment approaches and improved management strategies for this condition.

Vascular Changes and Neovascularization

Ocular rosacea is characterized by vascular abnormalities, including vasodilation and telangiectasia,[47] contributing to the characteristic erythema and flushing observed in this condition. These vascular changes are mediated by various factors, such as neuropeptides and inflammatory mediators, including substance P and calcitonin gene-related peptide, which can trigger the release of vasodilatory substances such as nitric oxide and promote angiogenesis.[53] The increased expression of VEGF and its receptors, particularly VEGFR-2, has been implicated in ocular rosacea's neovascularization and vascular hyperreactivity. VEGF acts synergistically with other growth factors, such as fibroblast growth factor (FGF) and platelet-derived growth factor, to enhance vascular permeability and endothelial cell proliferation.

Disrupting the normal balance between proangiogenic factors, such as VEGF and FGF, and antiangiogenic factors, such as endostatin and thrombospondin-1, contributes to aberrant vascular changes and inflammatory cell infiltration in ocular tissues. This imbalance is further exacerbated by the presence of proinflammatory cytokines such as IL-1 and TNF-α, which enhance the expression of adhesion molecules on endothelial cells, facilitating leukocyte extravasation and perpetuating inflammation.[61] Recent studies have highlighted the role of the microbiome, particularly the presence of Demodex mites and *B. oleronius*, in triggering immune responses that exacerbate vascular and inflammatory changes in ocular rosacea. The interaction between microbial antigens and TLRs on ocular surface cells initiates a cascade of inflammatory signaling pathways, including the activation of NF-κB and the production of MMPs, which degrade extracellular matrix components and further disrupt vascular integrity.[30] Addressing vascular pathology through anti-VEGF therapies, laser treatments targeting telangiectasia, and antiinflammatory agents is crucial to the management of ocular rosacea. These interventions can help alleviate the visible signs of the disease, reduce neovascularization, and improve ocular surface health, ultimately enhancing the quality of life for affected individuals.[30,53,61]

Related Dermatological Factors

While ocular rosacea can often parallel cutaneous rosacea, there are instances where their presentations may vary. Patients with facial rosacea may experience concurrent ocular involvement, and the severity of the skin and eye disease can be correlated.[54,62] The pathophysiologic

mechanisms underlying the cutaneous and ocular manifestations of rosacea are likely shared as both conditions are characterized by altered innate immune responses, vascular dysfunction, and neurogenic inflammation.[53] TH17 cell–mediated immune responses play a role in rosacea, similar to other dermatological conditions such as psoriatic dermatitis. In these conditions, the recruitment of mast cells, driven by the upregulation of IL-17, is notable. There is an association between the severity of ocular findings, such as diminished visual acuity due to corneal involvement, and the presence of rhinophyma, papules, and pustules. During exacerbations of rosacea, paying special attention to ocular symptoms is crucial as the progression of skin disease can lead to severe ocular damage. Understanding the interdependent nature of dermatological and ophthalmological aspects of rosacea is essential to providing comprehensive and effective management strategies for individuals affected by this condition.[30,40]

MANAGEMENT AND TREATMENT

Because ocular rosacea is a chronic inflammatory condition affecting the eyes, often in conjunction with cutaneous rosacea, treatment should be done in stages according to disease severity and response to treatment. It can be divided into lid hygiene and lifestyle changes, topical treatments, systemic treatments, and other options such as complication management (Table 2).

Mild ocular rosacea is generally managed with key strategies that include lid and skin hygiene, lifestyle modifications, and the use of ocular lubricants. Patients are advised to clean their eyelids twice daily with nonirritating soap and apply warm compresses if eyelids are swollen. Sunglasses with UV filters can help mitigate photophobia and other light-induced symptoms. It is also important to eliminate any medications contributing to dry eye.[63] Skin protection is crucial, and patients should use physical barriers and reapply sunscreen every 3 to 4 hours. Replacing traditional soaps with nonirritating alternatives and using rosacea-specific skin care products can prevent flare-ups. These ocular and skin hygiene lifestyle changes are strongly recommended by several societies such as the ROSCO international panel, the National Rosacea Society Expert Committee, and the Rosacea Treatment guidelines of Switzerland.[64] Lifestyle changes include avoiding known triggers such as UV radiation, stress, warm climates, wind, heavy exercise, alcohol consumption, and hot or spicy foods, which can reduce symptoms.[65] Oral omega-3 fatty acids have shown benefits in improving tear film stability and reducing inflammation after 6 months of using 720 mg of eicosapentaenoic acid and 480 mg of docosahexaenoic acid per day. Both the ROSCO international panel and the National Rosacea Society Expert Committee have cited the use of oral omega-3 fatty acids as a strong recommendation and have proven its superiority over placebo in a randomized controlled trial (RCT).[32] The use of ocular lubricants with preservatives can alleviate dryness and discomfort in mild cases. However, for moderate cases, the continued use of preservative-free ocular lubricants is recommended to maintain ocular surface hydration and avoid additional damage related to eye drop preservatives.

For moderate rosacea, treatment should include what has already been mentioned for mild rosacea and topical medications should also be taken to control inflammation and prevent complications. The continued use of preservative-free ocular lubricants is recommended. Topical azithromycin (1%–1.5%) twice a day for 2 days or once a day for 5 days helps reduce inflammation and increases the quality and quantity of the tear film lipid layer.[64,66] Topical cyclosporine (0.05%–0.1%) twice daily and topical tacrolimus (0.03%) twice daily have been strongly recommended by several societies such as the ROSCO international panel, the National Rosacea Society Expert Committee, and the Rosacea Treatment guidelines of Switzerland. In independent RCTs, they have shown their superiority against placebo warm compress and artificial tears.[32] They can be used for long-term management, reducing inflammation and improving tear production, symptoms, and corneal staining, and are an effective alternative to corticosteroids without complications.[67] Lifitegrast 5% twice a day for 1 month has shown efficacy in improving MGD symptoms and corneal staining. Topical steroids are often required to reduce and halt ocular surface inflammation but are reserved for active inflammation unresponsive to other treatments. They should be used cautiously because of the risk of ocular complications such as ocular hypertension, steroid-induced glaucoma, and cataracts. Topical brimonidine might be an alternative to reduce ocular redness.[30]

For severe ocular rosacea, systemic treatments are often required to control the disease effectively. Oral doxycycline is the first choice for systemic treatment and has been strongly recommended by several rosacea societies or committees[32,64] and has shown efficacy in an RCT. However, there is no consensus on the initial and maintenance doses and treatment length.[68] Extended-release doxycycline at 40 mg per day is commonly prescribed. In more severe cases, an initial dose of 100 mg once or twice daily can be used for a couple of weeks followed by a tapered maintenance dose, and treatment typically lasts 12 weeks.[68,69] As an alternative to doxycycline, minocycline can be administered at 100 mg once daily for 12 weeks.[64] For patients who may not tolerate tetracyclines, oral azithromycin 500 mg once daily for 3 days, or once weekly for 3 weeks, is a viable alternative that has shown efficacy in RCTs.[32] Oral erythromycin is a viable option for children with ocular rosacea, as well as oral metronidazole.[70] Systemic cyclosporine is reserved for severe nonresponder cases that require systemic immunosuppression.[64] Other topical cutaneous treatments that might be useful for ocular rosacea include low-dose isotretinoin, azelaic acid, metronidazole, and ivermectin.[30]

In addition to pharmacological interventions, other treatments may be necessary to enhance patient outcomes and manage complications. Intense pulsed light (IPL) therapy and thermal pulsation therapy to the eyelids can be effective in reducing telangiectasias and improving dry eye symptoms.[32] A recent meta-analysis on IPL shows that 1 to 3 IPL sessions accompanied by meibomian gland expression are

TABLE 2. Treatment Options for Ocular Rosacea

Treatment	Rosacea Severity			
	Mild	Moderate	Severe	Complications
Hygiene and lifestyle changes				
Ocular hygiene	•	•	•	
Clean eyelids with nonirritating soap				
Warm compresses				
Sunglasses with UV filters				
Avoid medications that induce dry eye				
Skin hygiene	•	•	•	
Skin protection with physical barriers				
Skin sunscreen				
Face wash with nonirritating soap				
Rosacea-specific skin care products				
Avoid known triggers	•••	•••	•••	
UV radiation, stress, warm climate, windy climate, heavy exercise, alcohol consumption, hot or spicy foods				
Topical treatment				
Preserved ocular lubricants	•			
Preservative-free ocular lubricants		•••	•••	
Azithromycin eye drops		•	•	
Cyclosporine eye drops		•••	•••	
Tacrolimus eye drops or ointment		••	•	
Steroid eye drops		•	•	
Systemic (oral) treatment				
Omega-3 fatty acids	•••	•••	•••	
Doxycycline			•••	
Azithromycin			••	
Minocycline			••	
Erythromycin			••	
Metronidazole			•	
Cyclosporine			•••	
Others				
Intense pulsed light		•	•	
Thermal pulsed therapy		•	•	
Conjunctival graft				•
Cyanoacrylate glue patch				•
Deep anterior lamellar keratoplasty				•
Penetrating keratoplasty				•
Fine-needle diathermy				•
Anti-VEGF eye drop or subconjunctival				•
Scleral contact lenses				•
Cutaneous treatments				
Low-dose isotretinoin				
Topical cutaneous azelaic acid				
Topical cutaneous ivermectin				
Topical cutaneous metronidazole				

Recommendation level according to several rosacea societies such as the ROSCO international panel, the National Rosacea Society Expert Committee, and the Rosacea Treatment guidelines of Switzerland: •: weak recommendations; ••: moderate recommendations; •••: strong recommendations.

effective at improving dry eye symptoms and sometimes dry eye signs.[71] In cases of corneal scarring involving the visual axis, deep anterior lamellar keratoplasty is an excellent option to improve the survival of the transplant and visual improvement can be observed with fewer complications than full-thickness keratoplasty. This is because ocular rosacea often carries a poor prognosis for full-thickness keratoplasty; corneal scarring frequently includes corneal neovessels and the chronic and recurrent inflammation of this disease. Antiangiogenic treatments can help manage telangiectasias and corneal neovascularization, and scleral contact lenses may improve visual acuity in cases of an irregular cornea or a corneal scar.[64] Furthermore, other surgical therapies in the setting of corneal perforation such as conjunctival flap, Tenon

patch graft, cyanoacrylate glue application, and tectonic corneal transplantation (anterior lamellar or full-thickness) may be required[72] (Table 3).

COMPLICATIONS AND PROGNOSIS

Inflammatory conditions of the cornea can lead to a range of complications that affect both ocular health and vision. Patients commonly present with chronic and recurrent red eye, blepharitis, and frequent styes, which represent the early sequelae of ongoing inflammation. One of the more serious sequelae is the development of interstitial corneal scar, often accompanied by corneal neovascularization. These pathologies can predispose patients to recurrent corneal ulcers, which, if left untreated or if inflammation persists, may lead to corneal perforation. Such progression poses a risk to vision and can result in low vision or even blindness in severe cases. In these advanced stages, corneal transplantation may become necessary.

Long-term management of corneal inflammation often involves the use of topical corticosteroids. However, they carry their risks: the development of ophthalmic hypertension and subsequent progression to steroid-induced glaucoma. In addition, there is the risk of cataract formation, which may arise from both the medication itself and the underlying inflammatory process. Although inflammation can often be controlled, the chronic nature of the disease means that patients are at risk of repeated episodes of exacerbation. In some cases, effective management can result in minimal long-term sequelae, allowing for relatively normal vision and quality of life. However, in some cases, the disease may progress to a point where corneal damage leads to visual impairment.

TABLE 3. Treatment Recommendations: Therapeutic Target and Mechanism of Action

Treatment	Therapeutic Target	Mechanism of Action
Ocular, lid, and skin hygiene	Skin barrier dysfunction	Multivariate
Topical treatment		
Azithromycin eye drops	Antiinflammatory and antibacterial	↓TNF-α, IL-1, IL-6, MMP-9s
Cyclosporine eye drops	Inhibition of immune-mediated inflammation	Inhibits T lymphocytes and cytokines (IL-2, TNF-α, IFN-γ)
Tacrolimus eye drops or ointment		Inhibits calcineurin, reducing T-cell activation and proinflammatory cytokines (IL-2, TNF-α, and IFN-γ)
Steroid eye drops		↓ IL-1, IL-2, IL-6; inhibits phospholipase A2
Systemic (oral) treatment		
Omega-3 fatty acids	Antiinflammatory	↓TNF-α, IL-1, IL-6, and eicosanoids
Doxycycline Azithromycin Minocycline Erythromycin	Antiinflammatory and antibacterial (skin barrier dysfunction)	↓TNF-α, IL-1, IL-6, MMP-9s, neutrophil chemotaxis
Metronidazole	Antiinflammatory, antioxidant, antibacterial	↓TNF-α, IL-1, oxidative stress
Cyclosporine	Inhibition of immune-mediated inflammation	Inhibits T lymphocytes and cytokines (IL-2, TNF-α, and IFN-γ)
Isotretinoin	Cathelicidin pathway, Demodex	↓ Cathelicidins (LL-37) TNF-α, IL-8, ↓TLR2
Others		
Intense pulsed light	Telangiectasia, meibomian gland dysfunction, antibacterial	↓ Vascular permeability,↑ meibomian gland function, antibacterial effects, collagen production
Conjunctival graft	Corneal perforation	Mechanical protection, stability, ↓ inflammation
Cyanoacrylate glue patch		Prevents leakage, stimulates epithelization
Tenon patch graft		Structural and vascular support, promotes healing
Deep anterior lamellar keratoplasty	Corneal scar	Replacement of corneal transparency, visual rehabilitation maintaining endothelial cells
Penetrating keratoplasty		Replacement of corneal transparency, visual rehabilitation
Fine-needle diathermy	Corneal neovascularization	Direct thermal coagulation
Anti-VEGF eye drop or subconjunctival	Corneal neovascularization	Anti-VEGF, inhibits neovascularization and vascular permeability
Scleral contact lenses	Corneal irregularities, scar, severe dry eye	Provides smooth optical surface, protects the cornea
Cutaneous treatments		
Topical cutaneous azelaic acid	Antiinflammatory, antibacterial (skin barrier dysfunction, periocular inflammation)	↓TNF-α, IL-1, IL-6, action against *Propionibacterium acnes*, ↓ oxidative stress
Topical cutaneous ivermectin	Immunomodulation, antiinflammatory, Demodex (skin barrier dysfunction)	↓TNF-α, IL-1, IL-6, IL-8, antiparasitic
Topical cutaneous metronidazole	Antiinflammatory, antibacterial (skin barrier dysfunction)	Inhibits neutrophil activity, reduce bacterial colonization

IFN, interferon; IL, interleukin; LL, 2 leucine (L) amino acids; TLR, toll-like receptors; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

PEDIATRIC OCULAR ROSACEA OR PEDIATRIC BLEPHAROKERATOCONJUNCTIVITIS (PBKC)

Alternative terms for PBKC include childhood or pediatric ocular rosacea, phlyctenular keratoconjunctivitis (PKC), staphylococcal blepharokeratoconjunctivitis, blepharokeratoconjunctivitis in childhood, and meibomitis-related keratoconjunctivitis. Despite these different names, they belong to the same clinical category, indicating a broad spectrum of similar conditions.[73] PBKC is a frequently overlooked, vision-threatening, chronic, and recurrent inflammatory condition of the ocular surface that affects children and adolescents. The clinical manifestations encompass chronic blepharitis, meibomitis, conjunctivitis, and corneal involvement, ranging from superficial punctate keratitis to corneal infiltrates with vascularization and scarring.[26,74] This multifactorial disease can naturally progress to irreversible corneal damage in up to 81% of affected eyes, potentially leading to leukoma formation, irregular astigmatism, higher order aberrations, stromal degradation, and corneal perforation (Fig. 4). Consequently, this can result in permanent corneal blindness or amblyopia in young patients.[75–77] A revised Delphi consensus has established standardized terminology and clarified the terminology and definition of the disease, with specific diagnostic criteria.[26] This initiative aims to reduce confusion in terminology and enhance an accurate diagnosis, thus lowering the rates of underdiagnosis and misdiagnosis.

Diagnostic Criteria

The PBKC Study Group consensus has proposed a definitive diagnosis of PBKC when at least 1 or more indicative symptoms (such as recurrent chalazia, ocular irritation, burning, tearing, chronic discomfort, photophobia, foreign body sensation, blurred vision, and red eyes) are present, along with at least 1 clinical sign from the lid margin (including meibomitis, meibomian gland dysfunction, inflammation, erythema, chalazion, and hordeola), the conjunctiva (such as hyperemia, conjunctivitis, and phlyctenules), and the cornea (including superficial punctate keratitis, phlyctenules, infiltrates, vascularization, pannus, thinning, scarring, and ulcer). Moreover, skin manifestations (such as flushing, facial erythema, papules, pustules, and telangiectasia on the forehead, nose, cheeks, and chin) may or may not be present in both patients with PBKC and PBKC-suspect patients.[26]

Patients with PBKC usually report red eyes, tearing, photophobia, ocular irritation, blinking, and foreign body sensation and may report a history of recurrent chalazia.[76,78–

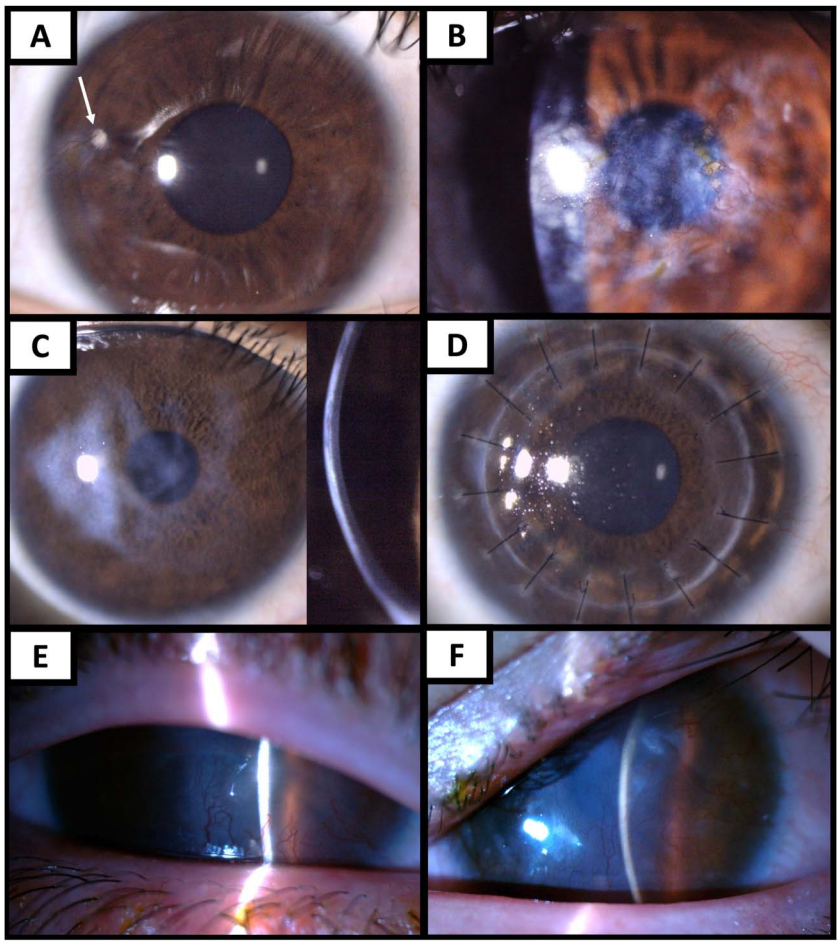

FIGURE 4. Representative images of patients with pediatric ocular rosacea or pediatric blepharokeratoconjunctivitis. A, The right eye of a patient with a marginal scar and neovascularization (arrow). B, The left eye of the same patient shown in A, with a more severe corneal scar with lipid deposits and neovascularization. C, Central corneal scar involving the anterior and middle stroma of an 8-year-old patient. D, The same patient as in C after deep anterior lamellar keratoplasty.

[80] The latter is highly suggestive of PBKC. PBKC is generally viewed as a bilateral condition, yet some patients exhibit notable asymmetry. In such cases, 1 eye may display ocular surface inflammation affecting the cornea while the other eye shows only mild symptoms confined to the eyelid margin. Eyelid margin alterations include scurfs, crusts, collarettes, meibomitis, meibomian gland dysfunction, and internal or external chalazion. Focal or diffuse meibomitis is a common feature of PBKC.[26] The most frequently observed conjunctival sign of PBKC is hyperemia. In addition, conjunctival papillae and follicular reactions are included in the diverse range of PBKC symptoms.

Superficial punctate keratitis is the earliest and most common corneal sign of PBKC, starting focally but sometimes spreading diffusely. It can cause punctate erosion, epithelial defects, and corneal vascularization. Severe cases may lead to central corneal scarring, vascularization, and visual loss.[26,76,81,82]

Epidemiologic Characteristics

PBKC is more common than often reported, particularly in pediatric eye clinics where it accounts for an estimated 12% to 15% of patient referrals.[83–85] However, most data come from tertiary eye care centers and may not accurately reflect the disease's true prevalence. Studies involving various ethnicities report on prevalence and severity but do not address differences between ethnic groups. Gender distribution shows a female predominance of up to 80% in some studies while others report no significant difference between men and women.[77,86,87] The mean age of onset ranges from 1 to 14 years, with diagnosis typically occurring between ages 3 and 9.[76] Identified risk factors include poor hygiene, seborrheic dermatitis, a history of atopy, Demodex mite infestation, and high detection rates of *Cutibacterium acnes* in meibum cultures.[74]

Differential Diagnosis

Many other inflammatory and infectious ocular surface diseases in children and adolescents can resemble PBKC clinically. Differential diagnoses include PKC, childhood ocular allergy, herpetic eye disease, adenoviral keratoconjunctivitis, and Thygeson superficial punctate keratitis. PKC is a distinct clinical entity induced by a type-IV Coombs and Gell hypersensitivity reaction to putative proteins from the cell wall of Mycobacteria, Staphylococci, Cutibacterium, and many other bacterial antigens.[73,74,80,88] In PKC, phlyctenules typically appear in the conjunctival limbal area and rarely affect the peripheral cornea, thus not causing major stromal vascularization or scarring. By contrast, PBKC-related phlyctenules involve the paracentral and central cornea, leading to prominent vascularization and substantial visual impairment.[80] It could be possible that patients with severe corneal involvement and affected vision in some published case series had PBKC rather than PKC. Herpes simplex keratitis can also resemble PBKC, leading to corneal stromal infiltration, scarring, and vascularization. Herpes simplex keratitis is primarily unilateral and typically lacks a history of eyelid inflammation, recurrent chalazia, meibomitis, or phlyctenules, which are common in PBKC.

Treatment Strategies

Treatment of PBKC is usually performed in a stepwise approach. Lid hygiene is the cornerstone of treatment and includes warm compresses and meibomian gland expression.[89] In addition, essential fatty acids have been extensively researched for their effectiveness in managing MGD and blepharitis. Jones et al[77] reported that 2.5 mL of daily flaxseed oil effectively prevented disease exacerbations in patients for whom the disease recurred when systemic antibiotics were discontinued. Lubricant eye drops are essential for PBKC to treat evaporative dry eye disease caused by MGD, address ocular surface hyperosmolarity, and reduce inflammation. For patients with PBKC with eyelid and ocular surface inflammation or those unresponsive to dietary changes, lid hygiene, and lubricants, topical or systemic antibiotics with antiinflammatory properties may be considered. Macrolides are the most commonly used antibiotics in these cases because of their dual antiinflammatory and antibiotic effects.[90,91] Similarly, topical corticosteroids are necessary during the acute phase of the disease to manage corneal inflammation and prevent neovascularization and scarring. In cases of severe ocular surface inflammation or patients recalcitrant to treatment, topical steroid-sparing regimens and systemic immunomodulation may prove beneficial.[83,92]

CONCLUSIONS

Ocular rosacea remains an underdiagnosed chronic disease with myriad manifestations and a yet unknown pathophysiology. The unique inflammatory microenvironment seen in ocular rosacea is a reflection of the immune disturbances associated with rosacea.

A multidisciplinary approach would be ideal as ocular rosacea frequently precedes the appearance of skin lesions. Pediatric ocular rosacea overlaps with PBKC; if left untreated, it can develop into sight-threatening complications. Clinical suspicion allows for an early diagnosis and precision diagnostics using genetic and molecular profiling, which promise to identify specific subtypes of the disease and allow for tailored treatment regimens. Treatment should include lifestyle changes, hygiene, avoidance of triggers, and local and systemic medication. There are many treatments and management alternatives, and a stepladder treatment approach is recommended. Emerging therapies, such as biologics and small-molecule inhibitors, aim to target the underlying inflammatory pathways more effectively than current treatments. These advancements, combined with a better understanding of environmental and lifestyle factors influencing the disease, hold the potential to improve patient outcomes and quality of life.

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