

# Ocular Rosacea—a Review

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Ocular rosacea, a disease often associated with acne rosacea, can present with a variety of clinical features, which are often nonspecific. However, in about one-third of cases, it may occur as an isolated entity without skin involvement. Appropriate diagnosis and management is essential as potentially sight-threatening corneal involvement can occur in a significant number of patients if the condition remains unrecognized and untreated. Diagnosis remains mainly clinical and includes recognition of the commonly occurring signs of chronic blepharoconjunctivitis, lid margin telangiectasis, meibomian gland dysfunction, dry eyes, and corneal involvement in the form of vascularization, infiltration, and even perforation. Management depends on the severity of the disease, with milder forms being amenable to treatment with local measures like lid hygiene and topical lubricants, while more severe forms require treatment with systemic drugs including tetracyclines, azithromycin, erythromycin, or metronidazole and more aggressive local therapy with topical steroids and/or topical cyclosporine. Surgical treatment may be required to manage the sequelae of chronic ocular surface inflammation.

## Keywords

Ocular rosacea, acne rosacea, meibomian gland dysfunction, tetracyclines, azithromycin, cyclosporine, omega 3 fatty acids, amniotic membrane

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Ocular rosacea is a chronic inflammatory disorder which may present in various manifestations such as chronic blepharoconjunctivitis, meibomian gland dysfunction, corneal vascularization, infiltration, scarring and, albeit rarely, even perforation. In nearly half to two thirds of cases it has been reported to occur in association with acne rosacea, a disease characterized by transient or persistent erythema, telangiectasia, papules, pustules, or phymatous changes affecting the convexities of the central face, particularly the cheeks, chin, nose, and central forehead.<sup>1,2</sup> In about 20% of cases, however, ocular involvement may precede skin involvement.<sup>2</sup> Potentially sight-threatening corneal involvement may be seen in up to one-third of patients.<sup>1,2</sup> This review aims to discuss briefly the clinical presentation, diagnostic criteria, newer investigation tools, and various treatment options of the disease.

## Epidemiology

- Rosacea is a chronic disease of middle age presenting usually between 30 and 50 years of age with a course of remissions and relapses.<sup>3</sup>
- Though reported more frequently in fair-complexioned people, its occurrence in dark-skinned individuals may have been underestimated because of the difficulty in identification of facial manifestations in such patients.<sup>4,5</sup>
- Facial findings are 2–3 times more common in females than in males, but the latter are more prone to develop phymatous changes.<sup>6</sup> However, ocular disease is equally distributed between both sexes.<sup>7</sup>
- Pediatric rosacea is an underdiagnosed entity because of the absence of facial features in many cases or because facial flushing may be mistaken for a healthy glow in children instead of being attributed to an underlying pathology.<sup>8</sup>

## Pathophysiology

The exact etiology and pathogenesis of rosacea has not yet been clearly defined, however, based on the spectrum of clinical findings, various hypotheses have been suggested. These include the following.

- Vascular component—it has been proposed that erythema, edema, and telangiectasia are caused by dilatation or incompetence of the blood vessels with the face being especially vulnerable because of its high vascularity. Significantly dilated blood vessels have been reported in all subtypes of rosacea.<sup>9</sup>
- Neurovascular component—this has been suggested to be an underlying mechanism on the basis of exaggerated skin sensitivity to noxious heat stimuli, which may be seen in these patients.<sup>10</sup>

Figure 1: A: Blepharitis of the upper lid; crusting of upper lid margin with matting of base of the lashes; B: Thickening of upper lid margin with telangiectatic vessels and rounding of the posterior border

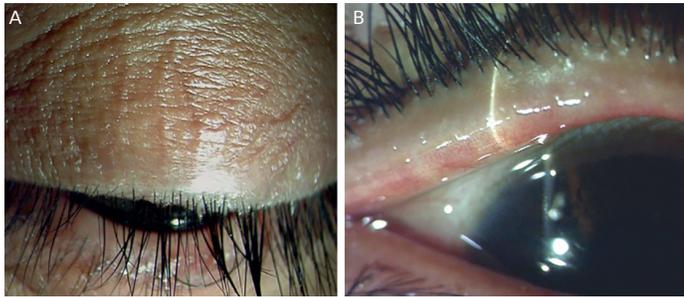


Figure 2: A: Pouting of ducts of meibomian glands (grey arrows) with papillofollicular reaction of upper tarsal conjunctiva; B: Clinical picture after treatment showing marked resolution of congestion and papillary reaction

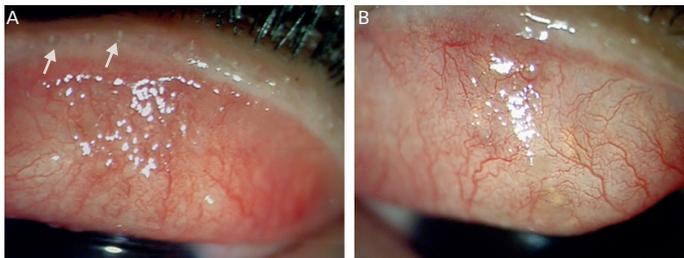
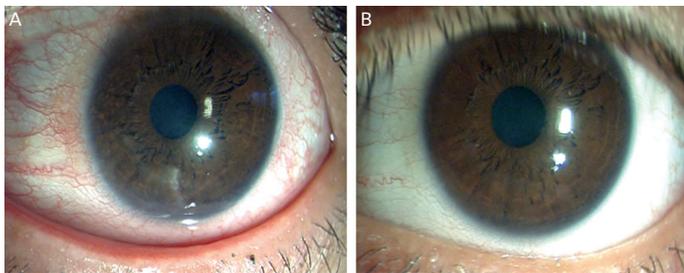


Figure 3: A: Congestion of bulbar conjunctiva; B: Resolution of bulbar congestion after treatment



- Inflammation—rosacea is considered to be an inflammatory disorder. Cathelicidins, a family of antimicrobial peptides involved in innate and adaptive immune response have been found in higher levels in rosacea affected skin,<sup>11</sup> with cathelicidin LL-37 in particular being implicated in the pathogenesis. Proinflammatory cytokines like interleukin (IL) 1 $\alpha$ , matrix metalloproteinase (MMP) 8, MMP 9 and tumor necrosis factor (TNF)  $\alpha$  levels have been found to be elevated in the tears,<sup>12,13</sup> while levels of IL-10, an anti-inflammatory cytokine, are depressed in patients with rosacea.<sup>14</sup> Vascular endothelial growth factor (VEGF) and its receptors have also been found in higher concentration in the skin of rosacea patients.<sup>15</sup> Despite these mediators having been identified, the primary initiating mechanism for inflammation is still not clear.

- *Demodex* infestation—*Demodex folliculorum* mites have been found in higher densities in skin scrapings or superficial standardized skin biopsies of patients with rosacea, and a decrease in mite density after treatment has been reported.<sup>16,17</sup> *Demodex* infestation may lead to activation of immune mechanisms or it may act as vector for other microorganisms such as *Bacillus oleronorum*, which can secondarily incite inflammatory response by activation of Toll-like receptors.<sup>18</sup>
- Genetic predisposition—as rosacea often affects multiple family members, a genetic component is suspected, although the genetic basis is still not clear.<sup>19</sup> Positive family history may be found in up to one third of patients with pediatric rosacea.<sup>20</sup>
- Environmental and lifestyle-related factors, for example, harsh climate, prolonged exposure to sunlight, alcohol, and spicy foods<sup>21</sup> are also considered to predispose individuals to the occurrence of rosacea.

It is likely that an underlying genetic predisposition becomes manifest on exposure to environmental factors. Gene dysregulation may also be responsible for the derangement in inflammatory mediators and/or instability of the neurovascular component.

### Clinical manifestations

Ocular manifestations are usually bilateral, but are often nonspecific. For this reason, the condition may remain undiagnosed or underdiagnosed, especially if the skin findings are subtle. Interestingly, a correlation between the severity of cutaneous and ocular findings has not been established.<sup>22,23</sup> Thus, a patient with subtle skin changes may present with severe ocular involvement and vice versa.

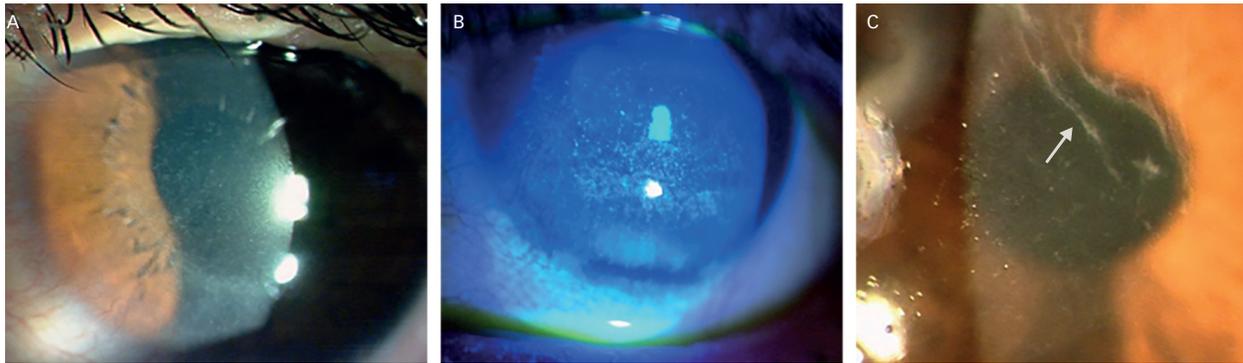
### Symptoms

Common ocular symptoms reported by patients with ocular rosacea are: foreign body sensation, eye strain, burning, irritation, redness of the eyes, or photophobia.<sup>22,24</sup> Rarely, a patient can present with blurred vision because of dry eye and/or corneal involvement. Chronic epiphora secondary to punctal stenosis because of the underlying chronic ocular inflammation may be another presenting symptom.<sup>25</sup> Secondary infections can also occur in a compromised ocular surface with a case series of fungal keratitis having been described in patients with ocular rosacea who were on treatment for long periods with oral doxycycline and intermittent topical steroids.<sup>26</sup>

### Signs

Frequently seen ocular signs in varying combinations are blepharitis (Figure 1A), telangiectasia over the lid margins, which often leads to thickening of the lid (Figure 1B), meibomian gland dysfunction and papillofollicular reaction of the palpebral conjunctiva (Figure 2A and B). Other common signs are injection, mainly in the interpalpebral bulbar conjunctiva (Figure 3A and B), posterior displacement of meibomian gland orifices, excessive seborrhoeic secretions, collarettes around the eyelashes, and lid margin irregularity.<sup>27</sup> Patients, especially those in the pediatric age group, may also present with recurrent hordeola and chalazia due to meibomian gland dysfunction.<sup>28,29</sup> Sight-threatening complications can occur because of corneal involvement in the form of punctate keratopathy (Figure 4A and B), irregular corneal epithelium (Figure 4C), corneal vascularization (Figure 5C) infiltration, ulceration, and, rarely, perforation (Figure 5B, D–F).<sup>30–33</sup> Cutaneous rosacea can be present in form of erythema, telangiectatic vessels, or papules over the central face including forehead, cheeks, nose, and chin which can be associated with rhinophyma of nose in

**Figure 4:** A: Punctate corneal epitheliopathy; B: Fluorescein staining showing significant punctate epitheliopathy; C: Irregular corneal epithelium (white arrow)



adults (Figure 5A). Cicatricial conjunctivitis mainly affecting the lower eyelid and symblepharon formation after conjunctival surgery has also been described.<sup>30,34,35</sup> Patients with ocular rosacea often have an unstable tear film, as demonstrated by a decreased tear film break up time (TBUT), punctate keratopathy and decreased Schirmer test values.<sup>36</sup> Corneal thickness is also reportedly decreased in patients with ocular rosacea, perhaps secondary to the defective tear film, with studies reporting a good correlation between tear film break up time (TBUT) and corneal thickness.<sup>37,38</sup> In a recent study, Ocular Response Analyzer in ocular rosacea patients has shown poor biomechanical properties of cornea with lower corneal hysteresis and corneal resistance factor compared to healthy individuals. However, corneal topographic findings, mean Goldmann IOP (Intraocular pressure) and corneal compensated IOP have been found to be similar in both groups.<sup>39</sup> Tear film osmolarity has also been found to be increased in ocular rosacea patients, which suggests meibomian gland dysfunction in such patients.<sup>40</sup>

### Pediatric ocular rosacea

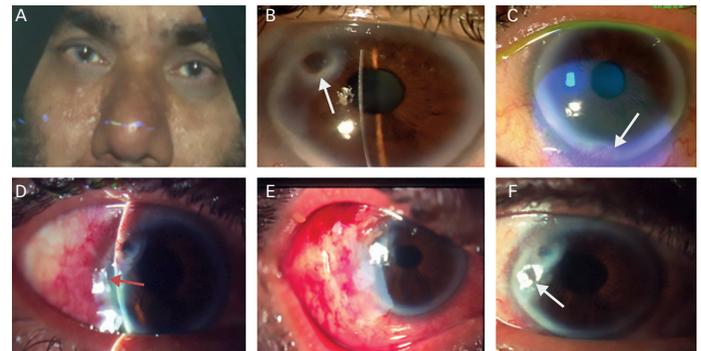
Pediatric ocular rosacea is often misdiagnosed because in nearly 55% of cases, ocular manifestations precede skin involvement.<sup>41</sup> Pediatric rosacea can present with bilateral disease, but asymmetric or unilateral manifestations in the form of chronic blepharoconjunctivitis, phlyctenular keratoconjunctivitis, or inferior punctate keratopathy can be seen<sup>29,42</sup> or a child may present with recurrent chalazia and hordeolum.<sup>29,41</sup>

### Diagnosis

To date, no diagnostic test for the confirmation of ocular/cutaneous rosacea has been introduced.<sup>43,44</sup> A high index of suspicion in patients with recurrent blepharoconjunctivitis, hordeola, chalazia, corneal infiltrates, thinning, or perforation without history of trauma or other definitive cause is hence crucial to correctly diagnose this condition, especially in cases without dermatological involvement. Symptomatic management without treatment of the underlying pathology may often be associated with an inadequate response. Certain diagnostic criteria have been laid down by the National Rosacea Society (NRS) expert committee wherein ocular rosacea has been classified as a separate subtype in addition to the other three subtypes of erythematotelangiectatic, papulopustular, and phymatous rosacea (Table 1).<sup>43</sup>

The NRS<sup>43</sup> has also classified ocular rosacea into three grades of severity (grade 1—mild, grade 2—moderate, grade 3—severe) (see Table 2).

**Figure 5:** Recurrent corneal melt and its management with fibrin glue assisted amniotic membrane transplantation using combined inlay and overlay technique



A: Facial photograph showing papules over the cheeks and rhinophyma of the nose. B: Old healed corneal perforation in the right eye previously managed with amniotic membrane grafting (white arrow). C: Fibrovascular pannus at 6 o'clock in left eye (white arrow). D: Area of peripheral corneal melt adjacent to the site of old healed perforation in right eye (red arrow). E: Inlay and overlay amniotic membrane graft applied over the area of corneal thinning using fibrin glue (white arrow). F: Healed area of corneal melt (white arrow).

### Diagnosis of pediatric ocular rosacea

Different diagnostic criteria have been given in different studies. Cetinkaya et al<sup>45</sup> have described pediatric ocular rosacea as a combination of meibomian gland disease, chronic blepharitis, recurrent chalazia along with long standing symptoms of ocular irritation, redness and photophobia which do not respond to routine medical treatment. A recent publication by Coimbra et al.<sup>46</sup> have given a proposed diagnostic criterion according to which if  $\geq 3$  of the five criteria are present (Table 3).

### Differential diagnoses

#### Children

Herpes simplex keratoconjunctivitis, chlamydial conjunctivitis, vernal keratoconjunctivitis, impetigo, limbal stem cell deficiency.<sup>29</sup>

#### Adults

Staphylococcal and seborrheic blepharo keratoconjunctivitis, meibomian gland dysfunction, dry eye, Stevens Johnson syndrome, cicatricial pemphigoid, atopic keratoconjunctivitis, eye involvement due to connective tissue disorders.

**Table 1: Diagnostic criteria for ocular rosacea<sup>43</sup>**

Two of the following
1. Facial rosacea*
2. Lid and conjunctival disease
3. Posterior blepharitis with chronic conjunctival hyperemia
4. Mixed papillary and follicular conjunctivitis with or without scarring
5. Corneal disease
6. Marginal ulceration with corneal thinning or perforation
7. Pseudopterygium or corneal vascularization
8. Coarse punctate infiltrates and scars
Associated non-diagnostic signs with ocular rosacea
1. Corneal and/or conjunctival phlyctenules
2. Episcleritis and/or scleritis

\*Primary signs of facial rosacea: transient or non-transient erythema, papules or pustules, telangiectasia in a central facial distribution; secondary signs of facial rosacea: burning or stinging sensation, elevated plaques, dry appearance of central facial skin, facial edema, phymatous changes.

**Table 3: Proposed diagnostic criteria of pediatric ocular rosacea by Coimbra et al.<sup>46</sup>**

1. Chronic or recurrent* keratoconjunctivitis and/ or red eye and/ or photophobia
2. Chronic or recurrent blepharitis and/ or hordeola/ chalazia
3. Eyelid telangiectasia documented by an ophthalmologist
4. Primary features of pediatric rosacea (facial convex areas with chronic flushing and/ or erythema and/ or telangiectasia and/ or papule, pustules in cheeks, chin, nose or central forehead and/ or primary periorificial dermatitis)
5. Positive family history of cutaneous and/ or ocular rosacea

\*Chronic (≥2 months); recurrent (≥3 episodes lasting >4 weeks in 12 months).

### Investigations

The diagnosis of rosacea remains mainly clinical, though certain investigations such as impression cytology,<sup>47,48</sup> confocal microscopy,<sup>49,50</sup> and meibography<sup>51,52</sup> can serve as an additional tools for managing these patients.

### Impression cytology of bulbar and palpebral conjunctiva

Impression cytology in ocular rosacea patients has shown epithelial metaplasia and decreased goblet cell density compared with normal subjects.<sup>47,48</sup>

### Confocal microscopy

*In vivo* confocal microscopy has been used to help quantify alterations in the cornea, meibomian glands, and cheek, as well as quantification of Demodex infestation in patients with confirmed rosacea-associated meibomian gland dysfunction-related evaporative dry eye.<sup>49</sup> Evidence of demodex infestation and increased mite density followed by reduction in density after adequate treatment has been demonstrated on reflectance confocal microscopy (RCM) of the cheek and forehead in patients with a clinical diagnosis of facial rosacea. Results of this study found RCM to be equivalent to superficial standardized skin biopsies (SSSB) in the diagnosis and follow up of rosacea patients.<sup>50</sup>

### Meibography

Ocular rosacea is associated with evaporative dry eye due to meibomian gland dysfunction and meibomian gland loss.

**Table 2: Severity grading of ocular rosacea**

Grade	Symptoms	Signs
Grade 1	Mild itching, dryness, or grittiness of the eyes	Fine scaling of lid margins; telangiectasia and erythema of lid margins; mild conjunctival congestion
Grade 2	Burning or stinging, crusting over lid margins	Definite conjunctival hyperemia; irregular lid margins with erythema and edema; chalazion or hordeolum
Grade 3	Pain, photosensitivity, or blurred vision	Severe lid changes, loss of lashes, severe conjunctival inflammation, corneal changes, with potential loss of vision; episcleritis, scleritis, iritis

can be objectively documented with Meibography and studies have reported higher meiboscores in ocular rosacea patients compared with healthy individuals.<sup>51,52</sup>

### Treatment

Treatment of ocular rosacea depends on the severity of the ocular manifestations as well as the association with systemic disease.

Lid hygiene using baby shampoo scrubs, warm compresses to express the meibomian gland secretions and tear supplements are the first line of treatment and are fairly effective. Lubricating gels or ointments are required for more symptomatic dry eye, while antibiotic ointments over the lid margins are helpful for anterior blepharitis.<sup>53,54</sup>

Oral tetracyclines are used as an adjunct therapy to topical agents<sup>55</sup> and are effective because of their anti-inflammatory (inhibition of MMP 9, a proinflammatory mediator) as well as antiangiogenic properties.<sup>56</sup> Other oral agents including azithromycin, erythromycin, and metronidazole have also been found to be effective, particularly for the pediatric patients or patients intolerant to doxycycline. The general principle during management of rosacea is to continue treatment for a long period (>3 months) with gradual tapering to prevent recurrences.<sup>57</sup>

### Tetracyclines

These are administered as a 500 mg tablet twice a day for 2–3 weeks and tapered according to the clinical condition. Side effects include gastric upset, photosensitivity, idiopathic intracranial hypertension, teeth discoloration, and liver toxicity.<sup>58</sup>

### Doxycycline

This can be prescribed as 100 mg once or twice daily for 6–12 weeks. Many patients may relapse after discontinuing treatment and hence require long-term maintenance therapy. However, this is associated with side effects such as diarrhea, nausea, vomiting, photosensitivity, and risk of skin burn. A lower dose of 40 mg (considered adequate for the anti-inflammatory action) has also been found to be effective for long-term maintenance therapy<sup>59,60</sup> and is, in fact, the only tetracycline which is US Food and Drug Administration (FDA) approved for use for up to 16 weeks in rosacea, with symptomatic improvement occurring by 6 weeks of treatment. In addition to the reduced incidence and severity of the side effects, the lower dose has not been shown to adversely affect the microflora of the eye and hence predisposes to a lesser risk of antibiotic resistance.<sup>60</sup>

## Minocycline

Minocycline is another drug in the tetracycline group which has also been shown to improve symptoms in moderate and severe meibomian gland dysfunction and rosacea, but it has side effects in the form of pigmentation of skin, nails, lips, teeth, conjunctiva, sclera, and other body surfaces.<sup>61</sup> The side effects usually occur when it is used in the dosage of 100–200 mg for as little as 1 year.

Tetracyclines, particularly doxycycline, is the mainstay of treatment for patients with moderate/severe disease or where patients are not relieved by topical medications; however, they are contraindicated for use in pregnant females and young children <8 years of age, as they have the potential to cause impairment in bone and teeth development and discoloration of the teeth (causing a grayish hue).<sup>62</sup>

## Azithromycin

Azithromycin, a macrolide antibiotic, has been found to be useful in disorders such as rosacea by virtue of its ability to inhibit production of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF  $\alpha$ , and leukotriene (LT) B<sub>4</sub>.<sup>63</sup> It has fewer side effects, better compliance and limited drug interactions. A study on the efficacy of azithromycin in patients with papulopustular rosacea with ocular involvement found improvement in skin lesions and eye symptoms with an oral dose of 500 mg per day for three consecutive days in a week, given successively for 4 weeks.<sup>24</sup> The best results of azithromycin are achieved at the end of 4 weeks and maintained until 12 weeks.<sup>64</sup> For prolonged effect, the drug may be used for several months in reduced dosages. A study comparing oral azithromycin with doxycycline for 3 months found both drugs to be equally efficacious, but the azithromycin group had more patients with diarrhea, while the doxycycline group had some patients who experienced epigastric pain.<sup>65</sup>

## Topical azithromycin

Topical azithromycin penetrates the tissues rapidly and remains for prolonged periods, thus requiring less frequent dosing and ensuring better compliance to treatment.<sup>66</sup> It can thus be considered as a treatment option for patients with ocular rosacea without skin involvement, avoiding the systemic side effects of doxycycline.<sup>66</sup> Azithromycin 1.5% drops have been shown to be effective for phlyctenular keratoconjunctivitis in pediatric ocular rosacea patients.<sup>41</sup>

## Erythromycin

Oral erythromycin can be used in pediatric patients where use of topical medicines is difficult. It is used in the dosage of 30–50 mg/kg/day for at least 3 months and on a long-term basis in case of recurrence.<sup>28</sup> Side effects include gastrointestinal disturbances and, consequently, azithromycin is preferred over erythromycin.

## Metronidazole

Oral metronidazole 20–30 mg/kg/day for 3–6 months can be used as an alternative treatment option, particularly in pediatric patients. Long-term therapy is avoided because of the risk of peripheral neuropathy.<sup>67</sup> Topical metronidazole gel has been effectively used for cutaneous lesions or anterior blepharitis.<sup>68</sup>

## Topical steroids

Topical steroids are recommended for short-term use in cases with non-resolving ocular surface inflammation, sterile corneal infiltrates, episcleritis, scleritis, and iritis.<sup>54</sup> Long-term use of steroids is associated with side effects

including glaucoma and cataract formation. Low-potency steroids such as loteprednol, fluoromethalone, and rimexelone are safer options, but long-term treatment should be avoided. In cases of relapse after withdrawal of steroids, the addition of topical cyclosporine as a steroid-sparing agent has been shown to be beneficial.<sup>68</sup>

## Topical cyclosporine

Topical cyclosporine is an immunomodulator that inhibits the activation of T cells and thus induction of inflammatory cytokines.<sup>69</sup> It has been used for ocular rosacea since 1980s. Arman et al.<sup>70</sup> found topical cyclosporine to be more effective than doxycycline in terms of symptomatic relief and improvement of tear production and stability, in patients with rosacea-associated ocular changes and dry eye complaints. Unlike topical steroids, topical cyclosporine A has a better safety profile and thus can be used for longer periods in patients with ocular rosacea.<sup>71</sup>

## The role of omega 3 fatty acids

Omega 3 fatty acids have been found to be effective for the treatment of meibomian gland dysfunction and dry eye.<sup>72</sup> There are limited studies on the efficacy of omega 3 fatty acids in ocular rosacea. A randomized controlled trial has demonstrated their role in alleviating patient symptoms and improving lid margin inflammation and meibomian gland function in patients with rosacea-associated dry eye, after treatment for a minimum of three months.<sup>73</sup>

Patients with milder form of the disease may be managed adequately with local measures like lid hygiene and topical drugs while those with moderate to severe disease may require systemic treatment and/ or topical steroids/ immunosuppressants on a long-term basis depending on the clinical need.

## Surgical treatment

Surgical treatment may be required for the sequelae resulting from chronic lid and ocular surface inflammation.

- **Incision and curettage** for recurrent chalazia.
- **Tissue adhesives such as cyanoacrylate glue**, along with bandage contact lens for small corneal perforations.
- **Amniotic membrane transplantation:** Amniotic membrane grafting has been found to be useful in cases of corneal ulceration and/ or descemetocoeles secondary to ocular rosacea by its anti-inflammatory properties and promotion of corneal epithelization.<sup>74,75</sup> Jain et al.<sup>33</sup> have reported successful use of amniotic membrane in ocular rosacea with peripheral corneal ulceration if cyanoacrylate glue fails to seal the perforation despite repeated attempts (*Figures 5B, D–F*).
- **Keratoplasty** either lamellar or penetrating may be required for larger corneal perforation and for optical purpose in cases of corneal opacities after the control of ocular inflammation. Tectonic lamellar keratoplasty has been found useful in cases with small to medium size corneal perforations. Larger central corneal perforations may require penetrating keratoplasty.<sup>76</sup>

## Future perspectives

The search for identifying a definitive diagnostic biomarker for rosacea in general, and ocular rosacea in particular, continues. Studies on the changes in glycosylation of tear and saliva in ocular rosacea patients have documented markedly increased numbers of sulfated O-glycans as compared to controls who predominantly had fucosylated N-glycans.<sup>44</sup>

Presence of sulfated O-glycans at levels higher than normal could possibly be used as a biomarker in the presence of signs and symptoms suggestive of ocular rosacea. Research on flow cytometric analysis for inflammatory mediators/biomarkers, glycomics and gene sequencing may open new doors to understand disease etiopathogenesis and treatment modalities.

## Conclusion

A high index of suspicion, awareness of the myriad signs (e.g., lid margin telangiectasia, meibomian gland disease, chronic blepharoconjunctivitis)

and a thorough lid and ocular surface examination can reduce the number of patients with ocular rosacea who frequently remain undiagnosed. Mild disease can be effectively managed with local measures such as lid hygiene, application of antibiotic ointment for blepharitis, and tear substitutes. For chronic and moderate/severe disease, additional treatment with oral doxycycline, oral, or topical azithromycin, short-term topical steroids and topical cyclosporine may be required for controlling disease activity, as well as preventing recurrences. □

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