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REVIEW

Global Perspectives on Therapy for Noninfectious Conjunctival Hyperemia: A Narrative Review

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ABSTRACT

Conjunctival hyperemia is one of the most frequent ophthalmologic presentations and may adversely affect quality of life due to associated discomfort and aesthetic concerns. In many countries, the prevalence of noninfectious conjunctival hyperemia is increasing due to lifestyle factors and the shift to technology-based employment. Management of noninfectious conjunctival hyperemia is typically aimed at addressing the underlying cause while alleviating signs and symptoms. However, an underlying cause might not be identified, treatment may not immediately reduce redness, or residual redness might persist. Topical treatment options include lubricants, decongestants, antihistamines/mast cell stabilizers, and anti-inflammatory drugs. Among these, ocular decongestants provide effective short-term relief, but the use of α1- (phenylephrine, tetrahydrozoline) or mixed α1/α2- (naphazoline, oxymetazoline) adrenergic receptor agonists is associated with tachyphylaxis and rebound redness. A highly selective α2- adrenergic receptor agonist (brimonidine 0.025%) reduces ocular redness without evidence of tachyphylaxis over 29 days and with minimal rebound redness upon discontinuation; however, longer-term effectiveness has not been evaluated. Other unmet needs pertain to the management of noninfectious conjunctival hyperemia as an aesthetic issue and the need to educate patients about the risks of surgical eye-whitening procedures and national recalls. Region- or

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country-specific unmet needs include a lack of awareness of the need for clinical assessment and appropriate treatment of ocular redness. While many cases of noninfectious conjunctival hyperemia can be self-treated, unmet needs remain with respect to access to care and patient awareness/knowledge of safe and appropriate treatment options and the importance of clinical consultation. The development of management guidelines specific to noninfectious conjunctival hyperemia is warranted to address patients' clinical and aesthetic concerns.

Keywords: Conjunctivitis; Decongestants; Health services accessibility; Red eye; Redness; Venous engorgement

Key Summary Points
Noninfectious conjunctival hyperemia is an ophthalmologic presentation that has become more common due to lifestyle and environmental factors.
Management of noninfectious conjunctival hyperemia involves identification and treatment of the underlying cause, as well as control of the signs and symptoms; however, identification of the cause can be elusive, and residual redness may persist.
Conventional treatments consist of lubricants, decongestants, antihistamines/mast cell stabilizers, and anti-inflammatory drugs, and newer, targeted treatments that may have fewer limitations.
Aesthetics can be a concern for patients with noninfectious conjunctival hyperemia, and patients are increasingly seeking redness-relieving treatments to improve the appearance of their eyes.
Region- or country-specific challenges in the management of ocular redness vary based on etiology and manifestations and other factors such as available treatment options, socioeconomic and environmental conditions, and access to eye care.

INTRODUCTION

Conjunctival hyperemia, or redness resulting from dilation of the microvasculature in conjunctival tissue, is one of the most frequent ophthalmologic presentations [1–6]. Hyperemia may be a sign of infectious [bacterial, viral, or atypical (e.g., acanthamoeba)] or noninfectious conjunctivitis [2–4, 7, 8]. Conjunctival hyperemia may adversely affect patients' quality of life due to associated discomfort and aesthetic concerns [9]. Individuals with ocular redness are perceived as less attractive, sadder, and less healthy than those with a whiter eye [10], and conjunctival hyperemia may also be associated with alcohol consumption and the use of substances such as marijuana and heroin [11, 12]. Additionally, conjunctival hyperemia impacts patients due to its effects on social activities and work routines [4].

In patients presenting with noninfectious conjunctival hyperemia, management typically aims to address the underlying cause while also addressing signs and symptoms and may involve both non-pharmacologic (e.g., trigger avoidance, lifestyle changes, artificial tears, and lid hygiene) and pharmacologic approaches [8, 13–17]. However, in some cases, a cause of conjunctival hyperemia might not be identified [15], treatment of an underlying cause may not produce immediate cosmetic improvement, or residual redness might persist despite treatment.

The management of noninfectious conjunctival hyperemia includes ocular lubricants, ophthalmic decongestants, antihistamines, and anti-inflammatory drugs. Treatment practices vary across geographical regions based on differences in awareness, cultural trends, resources, and accessibility. This article aims to explore current global treatment options for noninfectious conjunctival hyperemia and the unmet needs in the management of this condition.

METHODS

PubMed was searched through January 8, 2025, using the following search string: ("ocular redness" OR "ocular hyperemia" OR "ocular

erythema" OR "red eye" OR "eye redness" OR "conjunctival redness" OR "conjunctival hyperemia" OR "conjunctival injection") in combination with one or more of the following search terms: treatment, management, drops, topical, burden, cosmetic, meta-analysis, "differential diagnosis", real-world, prescribing, recommendation, consensus, guideline, trend, pattern, challenge, option, decongestant, vasoconstrictor, over-the-counter, and nonprescription. Reference lists of selected articles were also reviewed. Articles relevant to the etiology, diagnosis, and treatment options for noninfectious ocular redness, as well as challenges in the management of this condition, were selected for inclusion in this narrative review. Articles not published in English were excluded. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. In the following sections we discuss common etiologies, assessment and diagnosis, treatment, and unmet needs and novel perspectives of noninfectious conjunctival hyperemia.

COMMON ETIOLOGIES OF NONINFECTIOUS CONJUNCTIVAL HYPEREMIA

Common etiologies of noninfectious conjunctival hyperemia are wide-ranging (Table 1) [2–4, 7, 8, 18–24]. Irritating external agents such as dust, wind, or a foreign body can cause an acute case of unilateral conjunctival hyperemia [3]. The most common causes of chronic or recurrent conjunctival hyperemia are dry eye disease (DED) and ocular allergy, with prevalence estimates ranging from 5% to 50% and 20% to 40%, respectively [3, 4, 25, 26].

Dry Eye Disease

DED is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis and accompanied by ocular discomfort and/or visual symptoms [17, 27]. Signs and symptoms typically presented by patients with DED include ocular discomfort, dryness, redness/hyperemia, discharge, itching, foreign body

Table 1 Common etiologies of noninfectious conjunctival hyperemia

Dry eye disease
Ocular allergy (e.g., seasonal allergic conjunctivitis, vernal conjunctivitis, atopic conjunctivitis)
Other ocular surface diseases (e.g., pinguecula, pterygium)
Ocular or systemic medications, including recreational drugs
Environmental and lifestyle factors (e.g., contact lenses, cosmetics, digital eye strain)
Intraocular or periocular conditions (e.g., thyroid eye disease, idiopathic orbital inflammation)
Systemic diseases (e.g., rosacea, autoimmune disorders)

Table developed using data from Tsubota K, et al. [18]; Cheung AY, et al. [8]; Bonini S. [3]; Jaros PA, et al. [19]; Frucht-Pery J, et al. [20]; Singh RB, et al. [4]; Jo CE, et al. [21]; Park RB, et al. [22]; Peragallo J, et al. [11]; Wolffsohn JS, et al. [7]; Riguetto CM, et al. [23]; Macovei ML, et al. [24]; and Frings A, et al. [2]

sensation, heavy sensation, pain, light sensitivity, and eye fatigue [18]. The course of DED is chronic and may be characterized by fluctuating symptom severity and/or a gradual increase in symptom severity over time [17]. DED is classified into non-mutually exclusive categories of aqueous-deficient and evaporative DED [28]. Both forms promote an ocular environment that triggers a range of proinflammatory responses, resulting in ocular inflammation and conjunctival hyperemia [4, 29]. Conjunctival hyperemia in patients with DED has been associated with high ambient temperature and low humidity [30].

Ocular Allergy

Allergic conjunctivitis includes seasonal/perennial allergic conjunctivitis, vernal conjunctivitis, and atopic conjunctivitis [8]. Signs and symptoms are typically bilateral and, in addition to conjunctival hyperemia, may involve itching, eyelid edema, and watery or mucoid discharge, among others. Along with itch, conjunctival hyperemia is one of the most bothersome symptoms of allergy [31]. In a survey of 500 US healthcare providers who administered outpatient care to at least one patient with allergic rhinoconjunctivitis per week, 24% of providers overall and 27% of ophthalmologists/optometrists identified "red eye" as a symptom that led most of these patients to seek medical treatment at their practices [31]. Seasonal/perennial allergic conjunctivitis is generally acute but recurrent and is frequently associated with allergic rhinitis and dry eye, whereas vernal and atopic conjunctivitis have a chronic course with acute exacerbations [3, 8].

Other Ocular Surface Diseases

Many other ocular surface diseases (OSDs) may present with conjunctival hyperemia, including degenerative growths of the conjunctiva that may become inflamed, such as pinguecula and pterygium, among others [3, 19, 20]. While uncommon, chronic ocular surface inflammation may result in fibrosis and the development of cicatricial conjunctivitis, characterized by conjunctival inflammation and scarring, and associated with anatomical and functional changes to the ocular surface [3, 32].

Pharmacologic, Environmental, and Lifestyle Factors

Drug-induced conjunctival hyperemia may result from the use or misuse of ocular medications or systemic medications (e.g., dupilumab, immune checkpoint inhibitors) and recreational drugs [4, 11, 21, 22, 33]. Factors contributing to conjunctival hyperemia with ocular medications include active ingredients, preservatives, pH, and drop load (i.e., number of drugs applied as eye drops) [4, 33, 34]. Topical medications used to treat glaucoma and ocular hypertension may cause OSDs and conjunctival hyperemia [35, 36]. Prolonged use of ocular decongestants that are α1- or mixed α1/α2-adrenergic receptor agonists can induce rebound redness upon discontinuation, possibly due to constrictor tachyphylaxis or vasoconstrictor-induced tissue ischemia with release of vasodilating mediators [9, 33, 37]. Long-term use of drugs containing the preservative benzalkonium chloride has been associated with cytotoxic effects that impact the homeostasis of the conjunctival surface and lead to chronic inflammation and cicatrization [4, 36, 38–41].

Environmental and lifestyle factors are additional causes of noninfectious conjunctival hyperemia. Irritant-based sources of conjunctival hyperemia that elicit an inflammatory response include cosmetics, chlorinated water, smoke, and other pollutants [4, 28]. Cosmetic procedures for the periocular area, such as cosmetic eyelash treatments (e.g., curling, tinting), botulinum toxin and filler treatments, and chemical peels, may adversely affect the ocular surface, as can surgical procedures such as refractive surgery and laser-assisted in situ keratomileusis [28, 42]. Conjunctival hyperemia may result from inflammation associated with contact lens use, especially if the patient is engaging in risky behaviors such as sleeping with the lenses in or wearing or sharing "party" lenses [28]. Contact lens wear can also contribute to the development of evaporative DED or

papillary conjunctivitis [27, 43]. In a survey conducted among adults in Saudi Arabia between October 2022 and April 2023, ocular redness was the most commonly reported contact lens-related adverse event, affecting 291 of 391 (74%) contact lens wearers [44]. Digital eye strain (or "computer vision syndrome") refers to a group of ocular and vision-related problems resulting from prolonged use of computers, tablets/e-readers, and cell phones [7]. Symptoms of digital eye strain can include ocular hyperemia as well as ocular tiredness/soreness, blurred vision, eye strain/pain, burning, tearing, ocular dryness, foreign body sensation, and light sensitivity [7, 45, 46]. Use of contact lenses may exacerbate digital eye strain by decreasing the frequency of blinking and affecting tear dynamics [46].

Other Factors

Intraocular (e.g., uveitis, postoperative inflammation) or periocular (e.g., thyroid eye disease, idiopathic orbital inflammation, eyelid malpositions, and lash disorders) conditions may also cause ocular redness and should be differentiated from conjunctival hyperemia [2, 3, 23, 24]. Ocular redness may also occur in the setting of systemic diseases such as rosacea and other autoimmune disorders [2, 3]. Ocular rosacea represents a major cause of conjunctival hyperemia, with ocular manifestations primarily involving the periocular skin, eyelids, conjunctiva, and cornea [47].

ASSESSMENT AND DIAGNOSIS

A comprehensive description of the assessment and differential diagnosis of conjunctival hyperemia is beyond the scope of this article and has been reviewed elsewhere [2–4, 13]. When assessing the patient with ocular redness, it is important to rule out emergency conditions that require immediate intervention, such as acute angle-closure glaucoma, corkscrew vessels from a carotid-cavernous sinus fistula, trauma-related globe rupture, viral disease such as epidemic keratoconjunctivitis or herpetic keratitis, scleritis, keratitis and corneal ulceration, and orbital cellulitis (Table 2) [2, 13, 48–50].

A targeted approach to determine the cause of ocular redness starts with detailed history-taking [1, 2, 4, 8, 51]. This should include timing of onset; unilateral or bilateral involvement; acute or chronic/relapsing onset; features and severity; recent exposure to an infected individual; history of trauma (high- or low-velocity); previous treatment or surgery; and the presence of associated symptoms such as itchiness, discharge, photophobia, or pain (presence and degree).

Subjective scales and automated tools for diagnosing and scoring conjunctival hyperemia are being adopted into clinical practice to facilitate accurate detection at initial presentation and enable comparisons over time during and following treatment [4].

TREATMENT

Table 3 highlights current topical treatments for managing noninfectious conjunctival hyperemia [9, 15–17, 33, 52–55]. Therapies for hyperemia will ideally restore normal tissue function while also addressing cosmetic concerns such as ocular redness. Ocular lubricants may provide temporary symptom relief for symptoms associated with DED or allergy [15]. Ophthalmic decongestants provide effective short-term treatment of ocular redness but do not target the underlying pathological mechanisms of OSDs. These agents may be considered to treat noninfectious and nonallergic conjunctival hyperemia due to minor irritation without apparent underlying etiology and can also be used on a short-term basis for mild cases or in conjunction with targeted systemic and/or ophthalmic medications (described in Table 3) to reduce ocular redness in patients with OSDs (e.g., allergic conjunctivitis, DED) [8, 9, 15, 33]. Topical antihistamines and mast cell stabilizers play a role in treating acute conjunctival hyperemia due to allergic conjunctivitis [15, 56]. Immunomodulatory and anti-inflammatory drugs may be considered in patients with chronic/relapsing forms of conjunctival hyperemia associated with persistent inflammation, presumably due to underlying immune dysregulation [15].

Table 2 Common red eye emergencies

Diagnosis	Relevant history and examination findings	Concerns and risks
Acute angle-closure glaucoma	Sudden onset of unilateral eye pain radiating to the periocular and frontal region Nausea Appearance of halos around light Diffuse red eye with ciliary flush Cloudy anterior chamber Unilateral "rock-hard" eyeball on palpation Markedly elevated intraocular pressure Pupil unresponsive to light	May lead to blindness within 72 h Transfer of anterior pressure to posterior eye compromises retina
Corkscrew vessels from a carotid-cavernous sinus fistula	Bilateral massive dilation of conjunctival and episcleral vessels Extraocular muscle enlargement Ipsilateral cavernous sinus enlargement Pulsatile exophthalmos Rushing sound in orbit audible on auscultation Vision deterioration Double vision Headache	Can cause rapidly progressive vision loss
Trauma-related globe rupture	Severe pain Peaked, tear-shaped pupil with hyphema Subconjunctival hemorrhage around cornea or iris Reduced visual acuity	Can cause permanent vision loss
Herpes zoster keratitis	Herpetic facial lesions (especially lesion on nasal tip) Classic "tree branch lesion" (dendrite) with fluorescein	Lesion may cause scarring and permanently impair vision
Active scleritis	Reduced visual acuity Severe pain Photophobia may occur Deeper injection than episcleritis, multiple quadrants may be affected	Scleral ulceration and perforation may occur May result in vision loss
Corneal ulceration	History of contact lens use Conjunctival injection Corneal opacity Foreign body sensation	Lesion may cause scarring and permanently impair vision

Table 2 continued

Diagnosis	Relevant history and examination findings	Concerns and risks
Orbital cellulitis	Antecedent sinus complaints External preseptal redness or swelling Impaired intraocular movement due to post-orbital edema with chemosis and proptosis	Secondary complications may compromise vision or be life-threatening

Table developed using data from McSwigan TM, et al. [50]; Frings A, et al. [2]; Lansingh VC, et al. [13]; Gonzalez Castro LN, et al. [48]; and Hayre A [49]

UNMET NEEDS AND NOVEL PERSPECTIVES

Despite the availability of a range of pharmacologic options for the management of noninfectious conjunctival hyperemia, several unmet needs remain (summarized in Table 4). These unmet needs relate to increasing demand, the shortcomings of currently available treatments, challenges associated with regional differences in clinical practice and access to eye care, and the need to educate patients about the importance of clinical assessment and the safety of various treatment options.

Prevalence

The prevalence of noninfectious conjunctival hyperemia in otherwise healthy younger patients has been increasing as a result of lifestyle factors. In particular, digital eye strain is increasingly a problem due to increased screen time associated with the use of smartphones, tablets, and computers/laptop monitors, as well as with gaming and the shift to technology-based employment [7, 57]. The global prevalence of digital eye strain is estimated at 70% [7]. An increase in digital eye strain and DED symptoms in association with lifestyle factors and the shift to technology-based employment has been reported across countries worldwide [46, 58–60]. Another contributing lifestyle factor is the increasing use and overuse/misuse of contact lenses. The global market for contact lenses is projected to grow by 5–7.5% per year, driven by increases in the number of people with myopia and in those with presbyopia choosing to wear contact lenses, as well as to an increased uptake of contact lenses in developing countries [61]. As lifestyle factors and technology-based employment are unlikely to change, an increasing need for treatment of noninfectious conjunctival hyperemia is anticipated.

Management

Management of ocular redness typically starts with the patient self-treating with OTC eye drops [14]. Artificial tears have demonstrated effectiveness in reducing allergen-stimulated conjunctival hyperemia, presumably by diluting and washing away allergens from the eye and acting as an allergen barrier [62]. Cold compresses are also effective at reducing conjunctival hyperemia resulting from allergy, which could indirectly reduce the infiltration of inflammatory mediators associated with the allergic response. A drawback to artificial tears and cold compresses is that they are most effective in the acute phase of an allergic response [62]. Dual-action antihistamines and mast cell stabilizers, such as alcaftadine and olopatadine, have been effective in reducing allergy-associated conjunctival hyperemia, with a prolonged duration of action [63–65].

Ocular decongestants in the form of α1- (phenylephrine, tetrahydrozoline) and mixed α1/α2- (naphazoline, oxymetazoline) adrenergic receptor agonists, widely used since the 1960s, have demonstrated efficacy in reducing conjunctival hyperemia, likely due to vasoconstriction of ocular blood vessels [9, 15]. Patients may use various combinations of ocular antihistamines and decongestants regardless of diagnosis and current recommendations in an attempt to achieve immediate relief. However, many of these eye

Table 3 Topical treatments for noninfectious conjunctival hyperemia

Category	Mechanism of action	Considerations
Ocular lubricants	Reduce tear osmolarity, dilute allergens and proinflammatory mediators, restore physiologic temperature of the eye, and partially restore ocular surface homeostasis	May aid both dry eyes and allergy Improve conjunctival hyperemia among other benefits, but provide only temporary symptom relief Artificial tears with higher viscosity (gels) may provide extended effectiveness but are potentially associated with reduced tear clearance and blurred vision Long-term use not effective for patients with severe symptoms
Ophthalmic decongestants: α1- (phenylephrine and tetrahydrozoline) or mixed α1/α2-adrenergic (naphazoline and oxymetazoline) receptor agonists	Induce vasoconstriction of blood vessels supplying eye via stimulation of α1/α2-adrenergic receptors	Well-established short-term efficacy for conjunctival hyperemia Long-term use limited by tachyphylaxis, rebound redness, and systemic side effects; thus, should only be used for short-term treatment (a few days)
Ophthalmic decongestants: α2-adrenergic receptor agonist (brimonidine tartrate 0.025%)	Induces vasoconstriction of blood vessels supplying eye (predominantly venules) via selective stimulation of α2-adrenergic receptors	No tachyphylaxis over 1 month and minimal rebound redness upon discontinuation Long-term studies needed to assess potential induction of ocular allergy Preservative-free formulation in development
Antihistamines/mast cell stabilizers	Selectively block H1 histamine receptors, inhibit degranulation of sensitized mast cells, and prevent release of inflammatory mediators (including histamine) from mast cells; block both early and late phases of allergic response	Appropriate for allergic conjunctivitis but not dry eye disease First-generation antihistamines provide redness relief for < 4 h and are associated with risk of significant systemic side effects (e.g., sedation) Topical antihistamines contraindicated in patients at risk for angle-closure glaucoma Several weeks of use required for optimal benefit of mast cell stabilizers

Table 3 continued

Category	Mechanism of action	Considerations
Anti-inflammatory drugs: corticosteroids	Increase lipocortin A synthesis, inhibit local leukocyte adhesion and chemotaxis, and inhibit systemic inflammatory responses (e.g., vasodilation, vascular permeability)	Long-term use limited by increased risk of infection, elevated IOP, induction of exacerbation of glaucoma, cataract formation, delayed wound healing, and (in some cases) corneal thinning Close monitoring required to avoid potential adverse events
Anti-inflammatory drugs: NSAIDs	Inhibit prostaglandin synthesis	Long-term use limited by potential for significant corneal toxicity (e.g., corneal thinning and melting)
Anti-inflammatory drugs: cyclosporine	Suppresses cell-mediated immune response and reduces inflammatory cytokine production via selective inhibition of IL-2 (required for transcription of T cells)	May be locally irritating or cause a burning sensation after treatment that may lead to cessation of therapy
Anti-inflammatory drugs: lifitegrast	Reduces swelling in ocular tissues, likely by inhibiting interaction between LFA-1 and ICAM-1, thus preventing T-cell activation and migration to target tissues	Used for treatment of dry eye disease Long-term safety (beyond 12 months) not established

Table developed using data from Singh RB, et al. [15]; Bielory L, et al. [33]; Rolando M, et al. [16]; Amescua G, et al. [17]; Burke J, et al. [52]; Hosten LO [9]; Ackerman SL, et al., [53]; DiVito M, et al., [54]; and Vollmer PM, et al., [55]

ICAM-1 intercellular adhesion molecule, *IL* interleukin, *IOP* intraocular pressure; *LFA-1* lymphocyte function-associated antigen 1, *NSAID* nonsteroidal anti-inflammatory drug

Table 4 Summary of unmet needs

Clinicians and resources to address increasing prevalence of noninfectious conjunctival hyperemia in younger patients who are otherwise healthy, due largely to lifestyle/technology factors
Ophthalmic medications that provide safe and effective long-term treatment of chronic/recurrent noninfectious conjunctival hyperemia without drawbacks such as tachyphylaxis, rebound redness, or ocular toxicities/complications
Development of clinical guidelines specific to the management of acute and chronic/recurrent noninfectious conjunctival hyperemia (in absence or presence of underlying ocular or systemic disease)
Need to identify and address patients' aesthetic concerns associated with ocular redness in the clinical setting
Efforts to increase awareness and knowledge about ocular redness, the importance of clinical assessment, and safe and effective treatment approaches
In certain countries/regions: increased access to ophthalmologists and to treatments for ocular surface diseases that may involve conjunctival hyperemia as a clinical feature
Need to caution against surgical eye-whitening procedures
Need to ensure that patients are aware of recalls and warnings pertaining to the use of OTC ophthalmic products

OTC over-the-counter

drops are not associated with long-term benefits due to their short duration of action, preservatives, tachyphylaxis, or rebound redness [9, 33]. Continuous use of α1- or mixed α1/α2-adrenergic receptor agonists presents a challenge in treating patients with chronic or recurrent disease. The development of tachyphylaxis through α1-adrenergic receptor desensitization and downregulation, which makes the treatment ineffective for long-term management, and rebound redness, which may worsen ocular redness upon discontinuation of treatment, have been described with ocular decongestants that are α1- or mixed α1/α2-adrenergic receptor agonists [9, 15, 33].

Newer therapeutic options for the treatment of conjunctival hyperemia associated with dysregulation of the conjunctival microvasculature may provide options for a safe "precision medicine"-like approach that specifically addresses microvascular dilation localized to targeted periocular tissues. In contrast to previous ocular decongestants (α1- or mixed α1/α2-adrenergic receptor agonists), brimonidine tartrate ophthalmic solution 0.025% is highly selective for α2 receptors relative to α1 receptors [52]. In an integrated analysis of data from four clinical trials, brimonidine tartrate ophthalmic solution 0.025% demonstrated significant improvement in ocular redness with no evidence of tachyphylaxis over 29 days of treatment and minimal rebound redness upon discontinuation [53]. The long-term effectiveness associated with real-world use of brimonidine 0.025% has not been characterized and remains an area for future investigation, given the absence of tachyphylaxis in clinical trials. A preservative-free formulation of brimonidine tartrate ophthalmic solution 0.025% is in development and has demonstrated efficacy, safety, and tolerability comparable to the original version with minimal rebound redness in a multicenter, randomized, active-controlled trial ($N = 380$) [66]. This formulation offers an alternative option of a preservative-free topical treatment to suit patient preference and sensitivity.

Additionally, the iatrogenic effects of topical steroids are an issue, as prolonged use may pose risks of infection, elevated intraocular pressure, development of glaucoma, and cataract formation, among other toxicities (Table 3) [15, 33]. In countries such as India, Eritrea, and Saudi Arabia, self-treatment for conditions such as conjunctival hyperemia with OTC ophthalmic steroids is prevalent and problematic, as it delays appropriate diagnosis and management and has been associated with adverse effects [67–69].

The US Food and Drug Administration issued recalls in 2023 for OTC lubricating eye drops from several major brands due to infection risk [70], and in January 2024 warned against the

use of unapproved copycat products that can be confused for brimonidine eye drops, as the counterfeit products may not contain brimonidine and pose a risk of infection [71]. Thus, it is imperative that patients are made aware of recalls and warnings pertaining to the use of OTC ophthalmic products.

While clinicians generally seek to treat the underlying cause of the inflammation of conjunctival vessels (e.g., allergic or infectious causes), conjunctival hyperemia may also occur in individuals without any evidence of ocular or systemic disease or during treatment of underlying issues [9, 15]. Even in patients with a known underlying cause of conjunctival hyperemia, a short course of medication for redness relief (e.g., with ocular decongestants) may be needed in combination with treatment for the cause of conjunctival hyperemia (e.g., antihistamines, antibiotics) [14, 72].

Aesthetic Considerations

Aesthetics can be a concern for patients with noninfectious conjunctival hyperemia, and patients are increasingly seeking redness-relieving treatments to improve the appearance of their eyes. Perception of an individual's healthy and aesthetically pleasing appearance has been a unifying trend across cultures, ethnic groups, and countries [73], fueling the need for global medical aesthetic practices that are safe and effective. Because the periocular region is one of the first areas of the body to show signs of aging, the eyes are frequently targeted for enhancement and rejuvenation [74]. Additionally, global trends such as the exponential growth of video conferencing and social media platforms that spotlight facial features, including the eyes and periocular region, have expanded the unmet need for interventions that restore and/or maintain a healthy, youthful appearance [73]. Some patients may not realize that aesthetic issues warrant discussion with their healthcare provider and may depend on unreliable sources (e.g., Internet, peers) for information rather than seeking advice on treatment from an ophthalmology professional.

Patient-centric care will need to consider the aesthetic components of health, including physical, mental, and social well-being [73, 75], in order to optimize patient-reported outcomes and satisfaction with treatment. Accordingly, there is a growing need for harmony in physician–patient relationships with respect to expectations and goals, as well as for a balanced therapeutic approach that restores normal tissue function while maintaining or restoring an aesthetically pleasing appearance. We recommend examining the patient's eyes directly, outside of the slit lamp, to assess their appearance and identify any redness. If conjunctival hyperemia is evident, then addressing aesthetic concerns with the patient is appropriate, for example, by asking whether the patient ever wishes that their eyes were less red. With the availability of several OTC options for redness relief, clinicians need to incorporate ocular aesthetics into their conversations with patients to help them select the right product. Education on the benefits and risks of the available OTC products, including the risk of rebound redness, is key in this regard. Table 5 highlights the conundrum of appropriate prescribing for aesthetic treatment of conjunctival hyperemia. The onus is on eye care professionals to consider patients' aesthetic desires while ensuring that they do not jeopardize their patients' ocular health in the name of beauty [74]. Conversely, clinicians should ensure that adverse cosmetic effects of therapies (e.g., for OSD or glaucoma) do not interfere with patients' compliance, thus compromising optimal clinical outcomes.

Evaluation, Diagnosis, and Patient Education

Challenges in the management of noninfectious conjunctival hyperemia vary in different regions of the world, based on etiologies and manifestations and other factors such as available treatment options, socioeconomic and environmental conditions, and access to eye care. No management guidelines specific to noninfectious conjunctival hyperemia or ocular redness were identified, highlighting an unmet need. Online guidance for patients from the

Table 5 Appropriate prescribing for aesthetic treatment of conjunctival hyperemia: a conundrum

Approaches to address conjunctival hyperemia may involve targeting the underlying medical condition and/or directly targeting redness (e.g., with ocular decongestants)
Global regions/countries differ regarding whether consumers can access redness relievers on an over-the-counter basis for aesthetic purposes
Scales or criteria to guide clinicians on appropriate prescribing of redness relievers for aesthetics are lacking
Based on our experience, we recommend:
Ensuring that any pathological cause for hyperemia is ruled out/treated or referred for surgical treatment if suitable
Addressing any aesthetic concerns with the patient if conjunctival hyperemia is evident upon examining the patients' eyes directly
Educating patients on the benefits and risks of available over-the-counter options for redness relief
Ensuring that adverse cosmetic effects of some therapies (e.g., for OSD or glaucoma) do not conflict with patients' aesthetic desires

OSD ocular surface disease

American Academy of Ophthalmology on the use of redness-relieving eye drops recommends only occasional and short-term (i.e., ≤ 72 h) use (including for brimonidine 0.025%) and notes the lower propensity for rebound redness with brimonidine versus other decongestants [76]. Patients should discontinue use and consult a doctor if their condition persists or worsens over 72 h [77]. A user-friendly hyperemia "screener" would be of value for general practice eye care providers (possibly incorporating artificial intelligence to guide diagnosis), along with hyperemia diagnosis and treatment guidelines that can quickly identify the most likely causes of "red eye" and rule out indicators of more severe ocular and systemic disease that will require an in-depth differential diagnosis and treatment plan.

Differences in treatment patterns are evident, based on clinical practice surveys from a limited number of countries. A survey of medical practitioners from Eastern Europe (Belarus, Bulgaria, Croatia, Czech Republic, Poland, Russia, and Ukraine) and the Middle East (Turkey, United Arab Emirates) conducted between May and September 2004 found that ocular redness accounted for approximately 15% of ophthalmology consultations [78]. Prescriptions were based on diagnosis (e.g., DED, allergic conjunctivitis), and ophthalmologists typically initiated therapy with artificial tears (30%); other topical treatments included antibiotics (21%), corticosteroids (6% alone, 17% in combination with an antibiotic), antihistamines/mast cell stabilizers (14%), and vasoconstrictors (5%). Among 840 patients visiting an eye clinic in Sari, Iran, between 2012 and 2013, ocular redness most commonly presented along with eye irritation (57%), followed by tearing (49%), eyelid swelling (30%), foreign body sensation (22%), ocular pain (22%), and itching (21%) [79]. Of the 188 patients (22%) with recent medication records, 107 (57%) took naphazoline, 85 (45%) received chloramphenicol, 67 (36%) used betamethasone, and fewer than 15% each used artificial tears, ciprofloxacin, or a corticosteroid; 39 patients (21%) used other medications. In a cross-sectional study of 3545 patients with allergic conjunctivitis from ophthalmologic centers across Italy, conjunctival hyperemia was reported in 85% of cases [80]. Overall, OTC decongestants/antihistamines (not specified if topical or systemic) were used by 43% of patients; other treatments included corticosteroids (41%), topical antihistamines (29%), systemic antihistamines (27%), mast cell stabilizers (15%), and antibiotics (6%). Treatment patterns were not consistent with recommendations; in particular, vasoconstrictor and corticosteroid use should have been lower [80, 81].

Awareness and knowledge about ocular redness, the need for clinical assessment, and safe and effective treatment approaches are lacking in some populations. A cross-sectional study of 500 adults attending an ophthalmology outpatient practice in Tamil Nadu, India, from January

to April 2022, found low levels of awareness (16% of patients) and knowledge about ocular redness [82]. When treating ocular redness, 42% of patients reported using OTC drugs from pharmacies, 28% used "home-based" treatment, 15% did not attempt treatment, considering the condition to be self-limiting, and only 14% of patients reported a need to seek medical attention. For infants/children with ocular redness, only 16–17% of adults sought medical attention, while 41% endorsed instillation of breast milk into the eye and 60% used OTC drugs. A survey of more than 1000 students (ages 10–21) from Sagamu, Nigeria, found that 81% had heard of "red eye" [83]. Although 85% acknowledged that a doctor treats red eye, respondents reported that they would self-treat their eyes using a variety of substances, such as onion and breast milk.

Surgical Considerations

There is a need to caution against surgical eye-whitening procedures such as I-Brite (Boxer Wachler Vision Institute, Beverly Hills, CA, USA), which can be associated with significant adverse events [84, 85]. This procedure typically involves resection of bulbar conjunctiva with or without removal of portions of Tenon's capsule, with concomitant and/or postoperative use of topical mitomycin C, an alkylating agent that inhibits synthesis of DNA, RNA, and protein [85–87]. Surgical eye-whitening has been associated with a range of complications, likely due either to the procedure itself or to mitomycin C, including but not limited to chronic conjunctival epithelial defects, DED, avascular zones in the sclera, diplopia requiring strabismus surgery, scleral thinning, and necrotizing scleritis [84, 85, 87, 88].

CONCLUSION

Noninfectious conjunctival hyperemia is a common condition that may result from minor irritation without an identifiable etiology or may occur in the context of an underlying disorder, most commonly allergic conjunctivitis or DED. Topical treatment with decongestants and/or antihistamines/mast cell inhibitors (in the case of allergy) may provide short-term relief of redness, but these drugs and other medications used to treat conjunctival hyperemia caused by OSD have important limitations. A selective α2-adrenergic receptor agonist (brominidine 0.025%) may address limitations associated with conventional ocular decongestants, but longer-term studies are needed. While many cases of noninfectious conjunctival hyperemia can be self-treated, unmet needs remain in many countries regarding awareness of when to seek medical attention for ocular redness and how to safely and effectively treat this condition. The development of diagnosis and management guidelines specific to noninfectious conjunctival hyperemia (i.e., establishing consensus among experts) is warranted to address patients' clinical and aesthetic concerns.

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Declarations

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