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ALLERGIC CONJUNCTIVITIS: A NEGLECTED DISEASE SHARING SYMPTOMS WITH CONJUNCTIVITIS DUE TO SARS-CoV2 INFECTION

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Abstract: Conjunctivitis is the major atopic disease affecting the ocular surface. The COVID-19 virus can cause ocular complications including conjunctivitis, though not necessarily in the early stages of the disease. Patients with seasonal ocular allergy also suffer from inflammation of the conjunctiva and are confused during the current pandemic as some symptoms can be similar to conjunctivitis due to COVID 19. The concrete differences between these two types of conjunctivitis has been highlighted in the review. As clinicians are grappling with questions about ocular manifestations of the disease, protective measures to reduce transmission, introduction of telemedicine has become essential in current scenario. Herein, we would like to offer a state-of-the-art description on mechanism concerning the ocular allergy from the immunopharmacological standpoint. At this respect, the role of Treg cells in ocular allergy needs to be explored, mainly because of their potential use in new immunotherapeutic approaches. Therefore, we aim to update the existing knowledge on pathology of the ocular allergy for further deepening its implication in allergen-specific therapy.

***Index Terms* - Allergy, COVID-19, Conjunctivitis, Receptors.**

I. INTRODUCTION

COVID-19 symptoms spiked mid-March as world came to terms with the emerging pandemic, but so did malady of overlying symptoms like ocular allergy. Ocular allergies share a lot of symptoms with highly-contagious conjunctivitis due SARS-CoV2 infection, and they both have impacted the conjunctiva [1]. It is necessary to be well-informed on the distinguishing factors of the two disease so that timely medical intervention can be sought.

While patients with respiratory viral infection with species D adenoviruses and subtype H7 influenza viruses possessing ocular tropism, suffer from the conjunctivitis [2], reports reveal that symptoms are most often mild and goes away without treatment within 1–2 weeks, it may last 2 or more weeks if complications develop [3]. Belser and colleagues had suggested that the eyes are a portal of entry for respiratory syncytial viruses, and the use of eye protection has been demonstrated to reduce the nosocomial spread of these viruses [4]. Although the reported incidence of both ocular symptoms and positive conjunctival swabs for SARS-CoV-2 has been limited but there remains high possibility for ocular transmission, with the conjunctiva as a conduit of infection. In the midst of the COVID-19 pandemic, symptoms of redness and itchiness in eye seem confusing and has given rise to widespread panic on the possibility of COVID-19 manifesting conjunctivitis even in patients with seasonal ocular allergy. Here, we will try elucidate the differential clinical entities and molecular events that occur in conjunctiva in both types of conjunctivitis based on available literature and then provide an algorithmic approach [5] to clinicians on how to safely manage patients with allergic conjunctivitis during the era of pandemics.

II. CLINICAL ENTITIES: OCULAR ALLERGY OR COVID-19

There has been usual surge in cases of benign allergic conjunctivitis as the rainy season approached and this disease that had earlier been considered inconsequential caused panic in patients as there were media reports on COVID-19 associated conjunctivitis, and the symptoms of allergic conjunctivitis overlapped with viral conjunctivitis associated with COVID 19 [6].

Most of the previously encountered coronavirus species including SARS-CoV and MERS-CoV infections rarely caused ocular conjunctivitis in humans [7]. However, conjunctivitis is associated with SARS CoV2 infection and reports suggest that some patients with COVID 19 infection suffer from typical symptoms including bulbar conjunctiva congestion and edema, accompanied by a large quantity of watery secretions and a small quantity of thin viscous secretions, an absence of follicles or pseudo-membranes formation, and lack of the corneal infiltration at the initial stage of infection, no decrease in vision, and no swelling of the lymph nodes near the anterior and posterior ear [8]. At late stages of infection, the symptoms of conjunctivitis included that found in early stages of infection along with corneal infection and involvement of peripheral infiltration with epithelial involvement [9]. The presence of virus in tear and conjunctival scrapings has been reported in patients with COVID 19 infection suffering from conjunctivitis and keratitis [10]. No case of uveitis has been reported [11]. Retinal disorders, such as retinal vasculitis, retinal degeneration and blood–retinal barrier breakdown had been reported in experimental studies [12]. Report on retinal findings in patients suffering from COVID 19 is rare and may be attributed to the failure at performing the retinal examination in the COVID-19 patients. However, very mild retinal microvascular abnormality involving the ganglion cell and inner plexiform layers of the retina is seen. Other major complications that might occur during this viral infection including punctate keratitis with sub-epithelial infiltrates, bacterial infection, conjunctival scarring and symblepharon, severe dry eye, irregular astigmatism, corneal ulceration with persistent keratoconjunctivitis, corneal scarring etc. [13]

Allergic conjunctivitis is a typical IgE- mediated allergic reaction. Allergy patients frequently experience an overlap of signs and symptoms. Dry cough, congestion, drainage and limited sense of smell might be overlapping, common symptoms of seasonal allergies and COVID-19, apart from symptoms of a low-grade fever, a bluish hue to the lids, mild angioedema (allergic shiner), fatigue, body aches, pains, and shortness of breath (patients suffering from ocular *allergies* having coexisting atopic manifestations such as rhinitis and *asthma) [14]*. However unlike allergic conjunctivitis, conjunctivitis associated with COVID 19 is associated with a watery discharge as well (which may feel slightly thicker and stickier than tears) [15]. People with allergic disorder, had been included in a higher risk group for coronavirus disease, but the available data showed that almost all of these patients were not severely affected [16].

Differential diagnosis of eye redness and increased tearing caused by allergic conjunctivitis needs to be done by clinicians with exclusion of viral/bacterial conjunctivitis, Herpes simplex virus keratitis, anterior uveitis, corneal abrasion, exposure keratopathy and chemosis in a critically ill patient. For this clinician need to be thorough about the patient's case history inclusive of information regarding the onset, duration, and characteristics of symptoms. Initially clinicians may conduct tele-optometric test using digital images from a portable slit-lamp camera for diagnosis. Later on anterior segment examination at the slit lamp with adequate protective measures can be used for confirming clinical findings. Measurement of visual acuity, intraocular pressure, and dilated fundus examination needs to be done to rule out more harmful ocular diseases. Where ever viral conjunctivitis is suspected RT-PCR with swab/tears needs to take by sweeping the lower eyelid fornixes to rule out SARS CoV 2 infection [17].

The diagnosis of allergic conjunctivitis is based on clinical history with the supportive test for identification of the specific allergen. However, it needs to be mentioned here that allergic conjunctivitis (seasonal and perineal) in general has no corneal involvement however corneal involvement maybe there in acute allergic conjunctivitis as diffuse punctate keratitis [18]. In cases of acute allergic conjunctivitis an intense and persistent follicular reaction, associated with mild to intense hyperemia is observed. The lacrimal puncta may be swollen or occluded by a cellular infiltrate with a consequent epiphora [19]. In vernal keratoconjunctivitis asymmetric tarsal involvement is often there. The limbal form has been characterized by Horner–Trantas dots [20]. Eyelid skin may be involved with erythema, swelling, and excoriation is observed in all types of allergic conjunctivitis.

III. WHEN TO SUSPECT THAT CONJUNCTIVITIS IS DUE TO COVID 19

In regions where community-level outbreak of COVID-19 is confirmed, every case of conjunctivitis with/without systemic symptoms should be considered as a probable case of COVID-19 and required test should be conducted. However, if the patient has known history of allergic conjunctivitis, therapeutic intervention with anti-allergics should be made [21].

Most of the ophthalmological diagnostic procedures could lead to transmission of COVID-19. Transmission of the disease through asymptomatic and symptomatic contacts has also been documented [22]

Direct and indirect fundus examinations, tonometry, slit lamp examination require close proximity with patients, thereby increasing the risk of exposure. Stringent infection control strategies at the health care level shall stop the spread of the disease and downgrade the risk of spreading the disease [23].

As per recent AAO guidelines, eye care practitioners should reduce the number of outpatient consultation days and elective surgical procedures, particularly in elderly patients and those with medical comorbidities (American Academy of Ophthalmology 2020). Telemedicine can be used in patients with known allergic condition [24]. Personal protection including PPE N95 mask, gloves during the corona pandemic outbreaks. Any ophthalmic consultation apart from acute cases should be deferred if the case is suspected to have COVID-19, till the infective status of the patient is confirmed [25].

Eye care providers are encouraged to use slit lamp breath shields and should counsel patients to speak as little as possible when sitting at the slit lamp to reduce the risk of virus transmission [26]. However, eye protection is recommended not only for all health care workers, but also for various categories of people at risk (e.g., immunocompromised patients/ allergic patients using corticosteroids located in small rooms with poor ventilation, or older people living in close communities, such as health care residences) and for individuals with ocular surface diseases (e.g., dry eye) or at risk of corneal ulcer (e.g., contact lens wearers) [27].

In case of accidental exposure to the fluid of the infected patient, eyes should be thoroughly washed with running water and the skin area should be properly cleaned with at least 70% ethyl alcohol-based cleaning solution for at least 20 s [28]. The person should be kept under quarantine till 2 weeks and required tests need to be conducted (Centers for Disease Control and Prevention 2020c).

IV. RECEPTORS AND THEIR ROLE IN THE PATHOGENICITY OF CONJUNCTIVITIS

Ocular surface cellular receptors are utilized by respiratory viruses like SARS CoV2 which is the Central phenomenon to COVID-19 pathogenicity the presence of ACE2 (*type I transmembrane metallocarboxypeptidase)* is critical to regulating processes such as blood pressure, wound healing and inflammation, via renin-angiotensin-aldosterone system (RAAS) pathway, throughout the body, including the eye [29]. RAAS has been used exploited beneficially in antiglaucoma drug development [30]. ACE-2 is an entry receptor for SARS-CoV-2 in eye. HSPG (heparan sulfate proteoglycan) act as assisting factor for ACE2 in endocytosis-mediated coronavirus entry and provide an environment of enrichment of the virus load close to the host cells through low affinity interactions [31]. The human ocular globe has its own intraocular renin-angiotensin system, which is present not only on the surface of the eye (e.g., conjunctiva and cornea), but also inside the eye including trabecular meshwork, aqueous humor, iris, ciliary body, non-pigmented ciliary epithelium, and retina [32]. TMPRSS2 is also highly expressed in various tissues, including conjunctival epidermis and cornea limbal stem cells, coexpression of TMPRSS2 and ACE2 making these tissues the virus entry point [33]. Ocular route thus becomes a dynamic ocular surface system with tear film influencing SARS-CoV-2 entry from the infected ocular surface to the respiratory and digestive tract through the lacrimal canaliculi [34]. The opposite passage of viruses from nasal mucosa to conjunctiva seems unlikely, but cannot be excluded [35]. There is respiratory-ocular mucosal immune interdependence with linkage via the nasolacrimal lymphoid tissue [36]. The corneal limbal stem cells may also allow these beta corona viruses to cross the ocular surface, and then spread from the eye to other parts of the body through the blood stream and/or the nervous system (ophthalmic branch of trigeminal nerve) [37], however there is no evidence on such route. In some animal models (feline and murine), beta coronaviruses can cause conjunctivitis, uveitis, retinitis and optic neuritis suggesting that it can penetrate deep inside the ocular globe [38]. Ocular cellular receptors contribute to tropism of virus and causing conjunctivitis during SAR CoV2 infection [39].

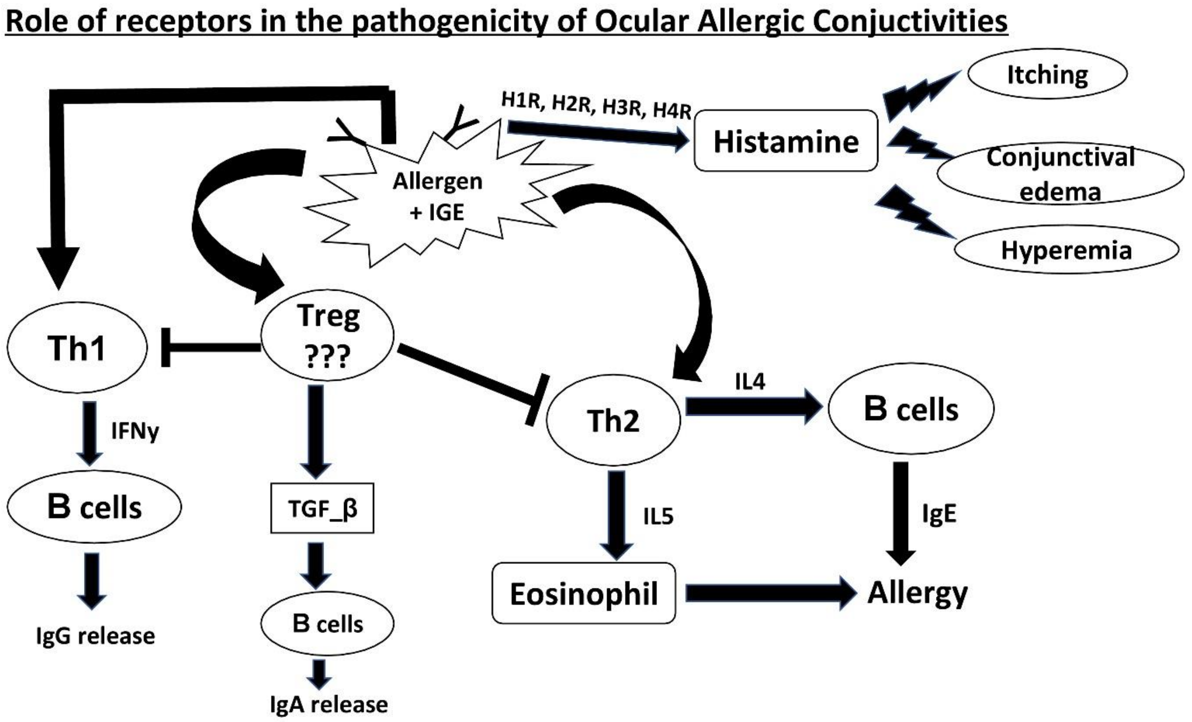
The mechanism of ocular allergy is totally different. Tear fluid of allergic patients have mediators like IgE antibody, histamine, leukotrienes and tryptase. Histamine, tryptase and bradykinin are immediately released following exposure to an allergen, release of mediators like leukotrienes and prostaglandins takes longer time [40]. Pruritus and conjunctival erythema, results from the release of histamine. Histamine acts through its cognate receptors like H1R, H2R, H3R, and H4R [41]. 5H1R which have critical role itching, conjunctival edema, and hyperemia by enhancing the vasodilation and vascular permeability and stimulating nerve fibers [42]. It also promotes pro inflammatory cytokine production by immune cells. H4 receptors mediates inflammatory responses in the allergic reaction [43]. In the conjunctival immediate hypersensitivity reaction histamine is released from degranulated mast cells and basophils in the early and late phases. Thus H1 and H4 receptors in conjunctiva can be biomarkers of allergic inflammation on the ocular surface [44]. The role of H4 receptors in the activation / modulation of the innate immune system cells such as epithelial cells, NK cells, antigen presenting cells and eosinophils needs to be considered in the future post covid therapeutic strategy [45]. Interleukins IL-4, IL-5, IL-6, IL-8, IL-13 produced by Th2 lymphocytes and activated TC mast cells present on the eye surface favor the maturation, migration, and activation of eosinophils [46]. The eosinophilic inflammation causes tissue damage through a variety of proteins released as cationic protein, most basic protein, peroxidase and neurotoxin, and is responsible for chronic allergic conjunctivitis [47]. Communication polypeptides, the cytokines, release helps mediate both early and late phase responses to the allergen; these are direct contributors to the observed signs and symptoms of ocular allergy. These polypeptides mediate most biological functions in the eye, and each cytokine is capable of multiple functions dependent on their location in the eye [48]. In tear film, cytokines have roles in homeostasis, mechanical stress, and immune response [49]. Cytokines IL-4 and IL-13 not only acts on Th2 cells and promotes IgE production but accelerates mucus secretion and chemotactic cell recruitment to areas of inflammation [50]. Th1 cells produce IFNγ have been shown to actively inhibit these cellular pathways and enhance IL12 production [51]. Reports suggest that IFNγ appears to contribute to the pathogenesis of allergic conjunctivitis in animal model at the effector phase, but not during the initial sensitization stage [52]. Other cytokines involved in inflammatory reaction during allergy include IL-1β, IL-2, IL-6, IL-8, IL-10, and TNFα [53].

In some forms of allergy, inflammation is mediated by lymphocytes, neutrophils and eosinophils there is no increase serum IgE or IgE in eye surface [54].

Recent experimental studies revealed that allergy-triggering molecules from dust mites can interact with an immune protein called SAA1, which is a sentinel against bacteria and other infectious agents [55]. This might be due to inappropriate immune triggering with immune system mistaking harmless allergens for infectious agents [56].

However, in the murine model of ocular allergy Treg have been found to be central to allergy modulation arising from hi-dose intraperitoneal sensitization [57]. This finding might promote the future use of hi-dose intraperitoneal sensitization although the role of tolerance and Treg in allergy modulation and misidentification in ocular allergies needs to be studied in details (Fig:1).

Figure:1



The figure depicts the role of specific receptors in ocular allergies and there is a probable action of Treg in combating allergies, however clinical studies required to confirm that.

V. WHEN DRY EYE AND OCULAR ALLERGY CO- EXIST

Allergic conjunctivitis may not be the only factor for seasonal discomfort. Studies indicate a clear seasonal pattern with respect to presentations of dry eye condition with prevalence of dry eye most common in the winter and spring and least common in the summer [58]. When an allergic conjunctivitis is associated with comorbidity it leads to "double trouble" [59]. When the eye is dry, allergies tend to be worse, and vice versa [60]. Therefore, clinicians need to be vigilant in their surveillance of of these comorbidities and modify treatment options accordingly. The tear film lipid layer plays an important role in retarding tear film evaporation and tear spillage [61]. Cellular entry of virus and adhesion might require lipid rafts and the presence of cell membrane cholesterol [62]. The cholesterol in tear lipid layer might act as "lipid raft", initiating viral adhesion. The detailed studies on lipophilicity of tears might explain how viruses access the ocular surface. Eyes with normal tearing the viral load is dispersed and may explain lack of conjunctivitis symptoms in many patients while in patients with dry eye the corneal and conjunctival epithelium may more easily retain the virus favoring a keratoconjunctivitis [63]. However, more studies on this subject is required.

It is often difficult to distinguish between dry eye and allergy as patient's symptoms are overlapping, however in case of allergy, the patient typically has tearing and itching and may report seasonal worsening or worsening when challenged by an allergen. If the patient has a red eye with boggy appearing conjunctiva, watery discharge and itching, allergic conjunctivitis is the diagnosis, on the other hand, if the symptoms appear subtler, and the eye does not appear very red but irritation persists, then clinicians need to suspect dry eye and differential diagnosis needs to be done for clearly establishing the disorder [64]. Again, a detailed patient's medical history is crucial after ruling out the viral infection. Clinically diagnosed allergic conjunctivitis with negative serum antigen specific and total IgE can be one form of dry eye [65].

Although the underlying mechanism is poorly understood studies point out to the involvement of other Th subsets, in addition to Th2 [66]. Severe forms of ocular allergy, might involve Th1 cells and IL-17 and Th1 thus acts as double edged sword [67]. Interleukins associated to Th1 stimulus (factor of tumour necrosis and interferon gamma) has been found to be associated with a decreased function of the goblet cells and consequent changes in the eye surface [68]. Thus patients with allergic conjunctivitis may suffer from the dry eye syndrome simultaneously.

The first generation antihistamines (like brompheniramine and chlorpheniramine) having small lipophilic molecules can cross the blood-brain barrier and inhibit the activity of the neurotransmitter acetylcholine, decreasing the secretion of mucus and widening airways, resulting in dry eye [69]. Second-generation antihistamines (Cetirizine, Levocetirizine, Loratadine), being more lipophobic, offer the advantages of a lack of CNS and cholinergic effects such as sedation and dry mouth, which are commonly seen in first-generation antihistamines (M A González , K S Estes 1998). However, the antimuscarinic action of the oral antihistamines Loratadine and cetirizine may diminish the aqueous phase of the tear film, leading to exacerbated signs and symptoms of dry eye [70].

Less tear production shall result in an inadequate flushing of environmental allergens from the ocular surface and increased concentration of inflammatory mediators on the ocular surface thereby worsening the symptoms of allergy [71]. So topical treatment is preferred in combating the morbidities associated with allergic ocular diseases [72].

VI. TREATMENT OF ALLERGIC CONJUNCTIVITIS

The main goals of the treatment include reducing the symptoms and minimizing the complications by controlling the inflammatory process. Option of telemedicine is preferred during pandemic era. The treatment should be addressed by a multidisciplinary team mainly involving clinician/ ophthalmologists and allergists for prompt diagnosis and treatment. Diagnosis of mild allergic conjunctivitis can be accomplished by skin tests with immediate reading, specific serum IgE tests or conjunctival provocation with allergens [73].

Lubricants help in clearing out of allergens from conjunctiva but must be free from preservatives, as they can cause epithelial toxicity and can aggravate allergies [74].

Topical antihistamines in the form of eye drops are indicated for the relief of symptoms, and act by blocking the histamine action on their receptors, particularly in the H1 receptors [75]. The side effects associated with the use of these drug are mydriasis and cycloplegia, as the drugs interact with muscarinic and alpha adrenergic receptors receptors [76]. Use of these drugs should be done with caution in patients at risk of angle-closure glaucoma [77].

Membrane stabilizers can be used in all types of allergic conjunctivitis but the onset of action is slow and they act by stabilizing the mast cell membranes by blocking the calcium channels preventing the release of histamine and activating the membrane enzymes thereby decreasing the inflammatory response and infiltration of inflammatory cells such as eosinophils, neutrophils and lymphocytes [78]. Double-action drugs (antihistaminic and membrane-stabilizing topical drugs) are now widely used and that reduce the immediate response by blocking the H1 receptors as well as the delayed response by stabilizing the membrane of mast cells with subsequent inhibition of activation and chemotaxis of eosinophils [79].

The use of topical corticosteroids can quite effectively reduce the entire inflammatory cascade of the allergic process, especially in chronic cases of allergic conjunctivitis [80]. However, prolonged use is associated to several complications [81]. Glucocorticoids that dissociate trans repression and transactivation are actively being pursued in order to better separate therapeutic and side effects [82]. Mapracorat, is a promising dissociated SEGRA (selective glucocorticoid receptor agonists) candidate for the treatment of allergic conjunctivitis [83]. This drug could prevent eosinophil accumulation and activation and induce eosinophil apoptosis in experimental studies [84].

The mechanism of action of immunomodulatory drugs (Cyclosporine and tacrolimus) occur through inhibition of the IL-2 receptors present on T lymphocytes and responsible for the activation [85]. They are considered substitute of corticosteroid therapy [86]. However, the prolonged use may lead to side effects and so should be used with caution [87]. Drugs like tralokinumab prevents allergy by targeting the IL-13 receptors on effector cells [88]. Research is needed on the application of this particular drug in ocular allergy. Utilizing cytokine-centric ocular allergy research for development of a drug that directly inhibits cytokine signaling on the ocular surface might be very interesting that could lead to the development of preventative eye-drops that greatly reduce the symptoms of ocular allergy [89].

The specific immunotherapy treatment based on the application of the allergen to which the patient is sensitized at increasing and continuous doses cannot be conducted with telemedicine alone. This therapy might require intermittent visit to allergy clinic. There are two main types of application: oral and subcutaneous. This treatment is practiced in patients with IgE-mediated disease detected after conducting skin tests with immediate reading or serum dosage of specific IgE [90]. Allergen specific immunotherapy appears to act through modulation of the Th2 response to the allergen, either by immune deviation of allergen-specific Th2 responses in favor of Th1 responses and/or through the induction of Tregs [91]. Tregs, down regulates pathogenic Th cell function and allergy immunotherapy is associated with Tregs augmentation in disease management [92]. Tregs suppress inflammation by upregulating immunosuppressive molecules and inhibiting the cells' tissue homing.

Studies have shown that sublingual immunotherapy reduced symptoms of ocular allergy [93]. Other Immunotherapy options include Intralymphatic immunotherapy and epicutaneous immunotherapy [94]. Immunotherapy is long term treatment option with proven efficacy which induces immunological tolerance specifically to the allergen used. So immunotherapy needs to be continued in patients who have already started the therapy.

VII. Discussion

Presently reports suggest that virus cannot be detected in the conjunctival sac of infected patients without conjunctivitis and the spreading of the virus through tears is low, nevertheless SARS-CoV-2 may survive for a long time or replicate in the conjunctiva, after conjunctivitis signs [95]. Patients with conjunctivitis who report to an optometry clinic, may be asked for COVID-19 test. As ocular allergies are rarely vision threatening and there is a decrease in level of air pollution due to quarantine personal contact with known allergic patients can be avoided [96]. According to the WHO cases classification schemes, patients can be grouped on the basis of triage system into general, suspect, and probable categories (World Health Organization 2003; Gavidia 2020). All patients should not attend the outpatient clinic to avoid personal and community spread of the disease. Triage should be performed and patients should be screened on the basis of:

A. Travel history in the last 2–3 weeks to any of the hot spots of COVID infections.
B. History of contact with known COVID-19 patient/suspect.
C. Symptoms of cough, cold, or fever.

Apart from the these each patient along with anyone accompanying the patient should be screened at the entrance for fever by the use of infrared thermometers (non-contact) by the security personnel or staffs by wearing adequate safety equipment (at least a mask) and hand sanitization of patient and their accompaniment should be done.
According to the triage system as described in the Table 1 [24], Category 1 can be categorized as general patients and can be seen on an outpatient basis, but with personal protective equipment (PPE). Categories 2 and 3 should be characterized as suspect/probable cases and only cases having ophthalmic urgency should be managed, in isolation ward with full protection. Rest non-urgent ophthalmic appointments should be rescheduled after 2 weeks.

Table:1 The triage system

Category	**Patient History**
1	Healthy patient with no travel history in 2-3 weeks.
2	Healthy patients with recent travel history /history of contact with COVID-19 patients.
3	Patients with signs of illness (cough, fever).

The advent of tele medicine and tele ophthalmology is a major boon for the patients suspected of COVID-19 and the patients requiring regular clinical evaluations as examination in the regular clinical set up is a challenge during this pandemic. The various avenues in this segment is discussed in the Table 2 [97]. Studies have recommended that slit-lamp bio microscopy of the periocular and ocular tissues, including high magnification assessment of the cornea and limbus, in moderate and severe disease [98].

Table:2 Avenues of telemedicine/ tele ophthalmology

Method	**Results**
The robotic remotely controlled stereo slit lamp system	Allows three-dimensional (3D) stereo viewing and recording of the patient's examination via local area network, Internet, and satellite.
Online Follow-up	The patients diagnosed and given a treatment regime should be followed up via telephonic appointments or video conferencing so that the need of travelling during the pandemic is reduced to a greater extent.

As per recent AAO guidelines, as a response to the state of national emergency due to COVID-19, eye care practitioners should reduce the number of outpatient consultation days and elective surgical procedures, particularly in elderly patients and those with medical comorbidities.

The precaution to be followed during the time of examination of the patients of category 1 are briefly described in the Table 3 [25-28].

Table:3 The precautions to be followed during the time of examination of the patients of category 1(Triage System)

Universal Precaution	-Use of surgical or N95 respiratory masks. -Use of gloves recommended. -Use of eye protectors whenever deemed necessary.
Hand Sanitization	-Repeated hand washing, using hand rub (0.5–1.0% chlorhexidine in 80% ethyl alcohol).
Personal Hygiene	-Change of gloves after handling every patients. -Avoidance of touching of face shields, mask, eye protective wear, face, head, and neck area before thorough hand wash.
Ocular Examination Modifications	-Barrier or breath shields to be used in Slit lamps. -All ophthalmic instruments should be disinfected using diluted household bleach, alcohol solutions containing minimum of 70% alcohol.
Examination Room Hygiene	-Keep doors open in the clinic rooms to avoid handling of the door knobs and to maintain ventilation. -Sanitization of door knobs and handles to be done at the end of each shift for precaution. -Weekly fumigation of the examination room is recommended.

The measures which should be taken for a patient who is suspected (or probable) to have COVID-19 (Categories 2 and 3) are described in the Table 4 [25-28].

Table: 4 The precautions to be followed during the time of examination of the patients who is suspected (or probable) to have COVID-19 (Categories 2 and 3)

COVID-19 Suspects	-For known cases of COVID-19, attending the patient on an outpatient basis is contraindicated due to high risk of cross infection. All consultations should be done inside quarantine or isolation wards. -Any ophthalmic consultation should be deferred in a case suspected to have COVID-19, till the infective status of the patient is confirmed. -If there is no ophthalmic emergency then the patient should be sent home or referred to the nearby COVID-19 testing centre or hospital for immediate follow-up.

Multi-disciplinary health care providers need to access to a growing selection of treatments available for allergic conjunctivitis and minimize the inflammatory cascade associated with the allergic response in order to provide relief of symptoms and to prevent complications associated with prolonged inflammation [99].

Laying the groundwork for understanding the molecular bio signature of ocular allergy is imperative for ensuring bigger-picture of research in this area and it should be based on factual and robust research [100]. This could improve diagnosis and may lead to the development of new testing methods for identification of allergic triggers that are non-invasive, cheap, and effective. The induction of a tolerant state in T cells is the key step in healthy immune responses to antigens in ocular surface. By gaining a deeper understanding of the heterogeneity of Treg populations involved in ocular allergy and the appropriate suppressive function system in inflammatory conditions, novel therapeutic approaches may be initiated (Fig:1). Tregs not only induce tolerance but also, when destabilized and reprogrammed, mediates pathogenesis, chonicity and severity of allegic disease. Studies have shown that Tregs could act as the nucleus in enforcing *healthy* immune responses to allergen as they are capable of suppressing T cells, Antigen presenting cells, and B cells by molecular secretion and cell-cell contact mechanisms. As detailed studies on Tregs can be helpful in pursuit of new therapy tools The reprogramming of Tregs in ocular allergy needs to be understood. Studies on development of hypoallergenic contact lenses to reduce the impact of allergens on the eye while functioning regularly to correct vision is also the need of the day. It would be be highly beneficial for contact lens-wearing subgroups suffering from ocular allergy.

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