Current Pharmaceutical Research (CPR)
Vol 1, Issue 4, October-December 2025
Journal Homepage: https://cpr.org.in/

Review Article

A Review of Allergic Conjunctivitis, Pathophysiology, Conventional and New Emerging Techniques for Treatments

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Keywords

Allergic conjunctivitis, IgE-mediated hypersensitivity, Mast cells, Antihistamines, Biologic therapy, Immunotherapy

Abstract

Allergic conjunctivitis is a common ocular disorder characterized by inflammation of the conjunctiva following exposure to environmental allergens and, in some cases, associated subconjunctival hemorrhage. It is primarily mediated by immunoglobulin E–dependent hypersensitivity reactions. Contact with allergens such as pollen, dust mites, or animal dander triggers mast cell activation, leading to the release of inflammatory mediators including histamine, leukotrienes, and prostaglandins. These mediators cause conjunctival vasodilation, increased vascular permeability, and recruitment of inflammatory cells, resulting in clinical manifestations such as ocular itching, redness, tearing, and swelling. Persistent or repeated allergen exposure may lead to chronic allergic conjunctivitis and complications such as papillary conjunctivitis. Management strategies traditionally focus on symptom control. Topical antihistamines alleviate itching and redness by blocking histamine receptors, while mast cell stabilizers prevent mediator release. Ocular decongestants provide short-term relief by inducing vasoconstriction, though prolonged use is discouraged. Corticosteroids are reserved for severe or refractory cases due to the risk of adverse effects. Recent therapeutic advances aim to address the underlying immunological mechanisms. Allergen-specific immunotherapy, including sublingual and subcutaneous approaches, has shown potential in reducing long-term disease severity. Biologic agents targeting key inflammatory pathways have emerged as promising options for severe disease. Additionally, innovative nasal-to-ocular drug delivery systems and experimental gene-based therapies are under investigation to improve efficacy and durability of treatment. Continued clinical research is essential to establish the safety, effectiveness, and long-term benefits of these emerging therapies.

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Article Info
Received: 09 December 2025; Received in revised form: 16 January 2026; Accepted: 16 January 2026; Available online: 21 January 2026; Volume: 1; Issue: 4; Pages: 509-523.

ISSN: 3049-2955/The authors © 2025, under exclusive license to the Sprout Publication.
DOI: https://doi.org/10.63785/2025.1.4.509523

1. Introduction

Allergic Conjunctivitis is a sequence of disorders initiated by an eye reaction to allergens in the milieu. They are pervasive, influencing from 10 to 20 percent of people everywhere. The amount persons with reactions grows each year, with 20% of people worldwide at present suffering from an allergy. Ocular symptomatology affects 40-60% of allergic individuals. Although Allergic Conjunctivitis worldwide has little effect on visuality, it produces a significant symptomatology and dramatically impairs the afflicted patients' quality of life, particularly for children and adolescents as some forms of the allergen affect them more frequently than others. Severe forms, on the other hand, can hurt images if they take a convoluted development and have consequences on the cornea, as this may in damage to the cornea and inflammation of the cornea. Due to this, those conditions must achieve prompt detection and therapy effectively to improve patients' quality of life, minimize the number of infections, and avoid serious side effects [1].

The symptoms are those that appear mostly in the primary or later stages of the disease. The phrase "tired" refers to the initial symptoms, which are Tearing, Itching, Redness, and Oedema (Conjunctival or Palpebral), which has been brought on by histamine coupling with its synapses, which was originally proposed by Fauquert. Mainly conjunctivitis is called 'Pink eye' disease it causes inflammation of the

Conjunctiva. The Delicate mucous membrane conjunctiva is the furrows within the skin around the eyes and the eyelashes where the sclera and cornea meet [2].

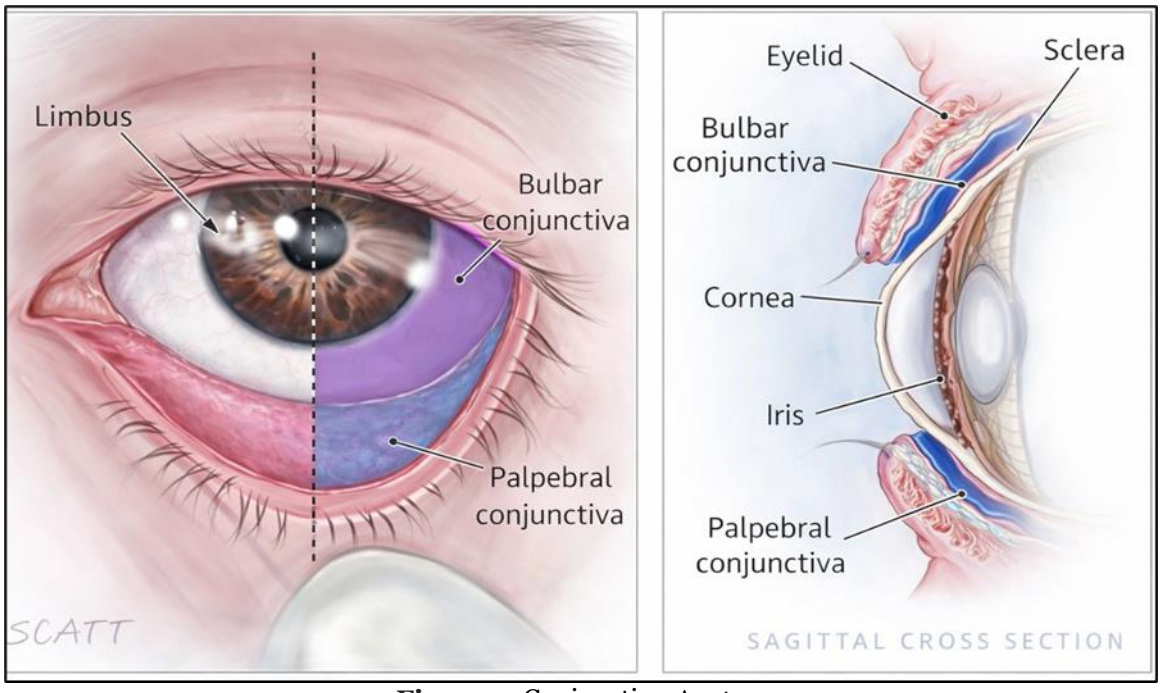

Figure 1: Conjunctiva-Anatomy.

Figure 1 illustrates the gross anatomy of the conjunctiva and its relationship with adjacent ocular structures. The left panel shows an external view of the eye highlighting the limbus, bulbar conjunctiva, and palpebral conjunctiva, demonstrating the continuity of the conjunctival membrane over the sclera and the inner surface of the eyelids. The right panel presents a sagittal cross-sectional view of the eye, clearly depicting the anatomical association between the eyelid, palpebral conjunctiva, bulbar conjunctiva, cornea, iris, and sclera. Together, the figure provides a clear anatomical overview of conjunctival organization and its role in protecting and lubricating the ocular surface [3].

Table 1 presents a comparative classification of conjunctivitis based on etiology and clinical characteristics, highlighting infective, allergic, and cicatricial forms. Infective conjunctivitis includes bacterial conjunctivitis, chlamydial conjunctivitis, granulomatous conjunctivitis, and ophthalmia neonatorum, which are primarily caused by microbial pathogens and are often associated with purulent discharge, conjunctival hyperemia, and potential contagion. Allergic conjunctivitis encompasses simplex allergic conjunctivitis, atopic conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis, all of which are mediated by hypersensitivity reactions and are characterized by itching, redness, tearing, and papillary changes of the conjunctiva. Cicatricial conjunctivitis represents a more severe category involving chronic inflammation and scarring of the ocular mucous membrane. Conditions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and secondary cicatricial conjunctivitis fall under this group and may lead to conjunctival fibrosis, symblepharon formation, and long-term visual impairment. Overall, the table underscores the diverse etiological spectrum and clinical severity of conjunctival disorders, emphasizing the importance of accurate classification for appropriate diagnosis, management, and prevention of ocular complications [4].

Table 1: Types of Allergic Conjunctivitis.

S. No.	Infective Conjunctivitis	Allergic Conjunctivitis	Cicatricial Conjunctivitis	References
1.	Bacterial Conjunctivitis	Simplex conjunctivitis	ocular mucous membrane	[5]
2.	Chlamydial Conjunctivitis	Atopic conjunctivitis	Steven Johnson syndrome	[6]
3.	Granulomatous Conjunctivitis	vernal conjunctivitis	Toxic epidermal necrolysis	[7]
4.	Ophthalmia neonatorum	Giant-papillary Conjunctivitis	Secondary cicatricial	[8]

2. Distinct kinds of conjunctivitis caused by allergies can be distinguished:

2.1 Viral conjunctivitis

Frequently, a virus that generates a common cold additionally develops viral conjunctivitis. Conjunctive inflammation indications may develop in themselves or unison with other types of symptoms of the cold, among them high temperatures, nose drainage, enlarged lymph nodes (sweat glands), and achy throat. Viral conjunctivitis coverages rapidly. It can be transmitted through touch, most commonly with objects that may have discussions with the injured somebody's corneal confessions. It can be spread through contact, for example, when a virus-infected person touches their eye and then touches another surface (e.g., a door handle) or swaps a possession that has attracted their fascination, perhaps a washcloth. Between 65% and 90% of cases of viral conjunctivitis are due to Adenovirus. Viruses have been responsible for Acute Conjunctivitis. When compared to test confirmation, impersonal accuracy in diagnosing viral conjunctivitis is >50 [9].

2.2 Bacterial Conjunctivitis

Bacterial conjunctivitis can be extremely contagious, commonly infecting several persons. Bacterial conjunctivitis is transmitted by touch, most commonly with objects that were brought into touch with the eye of the person who has affected fluids(fig.1) The bacteria can be spread through contact, for example, when a person with the Infection which fell into the path of the eye belonging to the affected person another surface (e.g., a door handle) or shares an object that has touched their eye e.g., Pillow cover. Several cases of bacterial conjunctivitis are undiagnosed. Acute bacterial conjunctivitis is mainly found in children, in more than 50% of cases [10].

Figure 2 Bacterial conjunctivitis of the human eye. The figure illustrates the typical clinical features of bacterial conjunctivitis, including marked conjunctival hyperemia, eyelid edema, and purulent or mucopurulent discharge accumulating along the eyelid margins. The inflammation of the conjunctival tissue results from bacterial infection, leading to dilation of conjunctival blood vessels and increased vascular permeability. Patients commonly experience symptoms such as redness, foreign body sensation, irritation, and crusting of the eyelids, particularly after sleep. The presence of thick discharge distinguishes bacterial conjunctivitis from viral and allergic forms. If left untreated, the infection may spread to adjacent ocular structures or become chronic, highlighting the importance of early diagnosis and appropriate antimicrobial therapy [11].

Figure 2: Bacterial Conjunctivitis in human eye.

2.3 Chlamydial conjunctivitis

This conjunctivitis is caused by the chlamydia bacteria &mainly occurs due to the sexually transmitted infection. Mainly this action affects sexually active adults & it can be transmitted into the newborn by their infected mother drug delivery. This infection affects the conjunctiva of the neonates and also the nasopharynx, lungs, rectum, vagina also urethra. It is an Acute Infection which is caused by the bacteria chlamydia trachomatis and it shows erythema, bruising of the lashes, palpebral conjunctivae, alongside bloody ocular disposal [12].

Figure 3: Chlamydial Conjunctivitis in human eye.

2.4 Seasonal allergic conjunctivitis
Among the most regular categories of visual sensitivities are off-season conjunctivitis associated with allergies (SAC, also known) and perennial allergic conjunctive disorders (PAC). Estimates vary, but these types of allergies are deemed to impact somewhere in the range of fifteen to fifteen percent of the overall population [13].

2.5 Perennial Allergic Conjunctivitis (PAC)
Unlike sac, PAC persists throughout the year and is usually caused by indoor allergens such as dust mites, pet dander, mold spores, and cockroach droppings. Symptoms; Similar to SAC, including itching, redness, tearing, and swelling [14].

2.6 Vernal Keratoconjunctivitis
VKC is a more severe and chronic form of allergic conjunctivitis that often affects young males. It is associated with a heightened allergic response and may be linked to atopic conditions like asthma and eczema. Symptoms; Severe itching, tearing, foreign body sensation, and light sensitivity. VKC can also lead to the formation of giant papillae on the inner surface of the eyelids [15].

2.7 Atopic Keratoconjunctivitis
AKC is a chronic and severe form of allergic conjunctivitis associated with atopic dermatitis (eczema). It tends to affect adults and can lead to significant eye damage if not properly managed symptoms**;** Intense itching, burning, tearing, and thickening of the conjunctiva. AKC can cause corneal complications [16].

2.8 Giant Papillary Conjunctivitis
Giant papillary conjunctivitis (GPC) is commonly linked to contact lens use but may also arise from exposure to various allergens. It is clinically defined by the development of enlarged papillae on the upper eyelid's inner lining. Symptoms; Discomfort, mucosal expulsion, appearance like you're swallowing foreign material, and obstruction to applying lenses for vision correction [17].

3. Epidemiology
Research has shown that the severity of eye-related allergy symptoms is often underestimated compared to nasal symptoms. However, recent nationwide surveys including Allergies Across America reveal that eye allergy issues rank very closely behind and sometimes even surpass nasal congestion as the chief complaint among allergy sufferers. The ISAAC Phase III study included 193,404 school-aged children between 6-7 years old from 37 countries and 304,679 teenagers between 13-14 years old from 56 countries. The study found that nasal symptoms associated with itchy and watery eyes were present in 2.2-24.2% of children and 4.5-45.1% of adolescents [18].

A validated self-administered questionnaire previously used to diagnose allergic conjunctivitis was distributed to 3,120 students aged 12-19 years old (with a mean age of 13.3 years) in school settings. Of the respondents, 1,293 individuals (41.4%) reported experiencing itchy eyes in the previous 12 months, and 1,371 (43.9%) reported excessive tearing. The sensitivity of this specific question was found to be 85.4%, while the specificity was 85.2% [19]. Through a survey and subsequent interviews, researchers estimated an allergic conjunctivitis cumulative prevalence of 19.1% among the studied population. Further, the combined prevalence of allergic conjunctivitis and allergic rhinitis was determined to be 17.6%, suggesting a comorbidity rate of approximately 92% between the two conditions [20].

In the comprehensive epidemiological investigation into individuals with allergies in Italy, approximately 40% exhibited symptoms potentially linked to allergic conjunctival disease. Meanwhile, in Japan, most of the population suffered from timber pollinosis, manifesting a multitude of manifestations, comprising sinus, vision, laryngo-pharyngeal, and superficial

visual cues [21].

Studies investigating the impact of genetics and environment on allergic diseases demonstrated associations between CD14 and CC16 polymorphisms in Finnish versus Russian Karelian women [22]. In Spain, a substantial proportion of patients in primary care reported nasal and ocular symptoms, with 83% experiencing symptoms either currently or frequently, and 36.4% indicating moderate to severe symptoms affecting daily activities. According to data from Sweden in the 1980s, 29 percent of respondents reported allergic symptoms in the nose. Of those presently experiencing symptoms, 64 percent were allergic to pollens and/or furred animals. Further, an extended ISAAC study demonstrated an increased prevalence of allergic rhino-conjunctivitis from 16.5 percent in 1985 to 29 percent in 2000. In a study in Switzerland, 93.3% of symptomatic patients diagnosed with hay fever exhibited conjunctivitis, while 92% had rhinitis. On average, the first signs of discomfort came during March and May, lasting an average of 2.7–1.8 months [23].

Even in developing countries with a lower prevalence of allergy, the ISAAC study reported Allergic Conjunctivitis in up to 20 percent of the population. In Nigeria, 39.2% of schoolchildren reported rhinitis associated with itchy eyes (allergic rhino-conjunctivitis). In France, the ARIA Allergic Rhinitis survey discovered ocular symptoms in 52% of allergic rhinitis patients. According to reports from Oxfordshire, United Kingdom, itching was found to occur at a higher rate than redness among survey participants. Redness was experienced more frequently than tearing. The prevalence in Turkey was 27.4%, with rhinitis at 11%, asthma at 10.2%, conjunctivitis at 7.1%, and skin diseases at 6.3% [24].

While the ISAAC study highlighted variations in rhino-conjunctivitis prevalence across centers, it did not clarify whether rhinitis and conjunctivitis had similar or differing prevalences. Statistics around the world on juvenile eyepiece abnormalities generally certain individuals., but nasal allergy incidences range from 12% to 34% across European countries. A recent analysis of NHANES III data in the USA showed that 40% of adults experienced ocular symptoms within 12 months, with no significant age-related changes. Around one-third of those receiving treatment showed discomfort shortly after being subjected to tobacco smoke, whereas exposure to cats elicited indications in around five percent of cases. A large national survey conducted in the United States highlighted the high frequency and importance of eye issues reported during the warmer summer months from May through August. Symptoms solely affecting the eyes were more common than issues only involving the nose alone. Among those suffering from hay fever or allergic rhinitis, eye symptoms happened by themselves (8%) or together with nasal problems (85.3%) more often than nasal symptoms without conjunctivitis (6.7%). This research indicated that eye issues were as bad as or worse than nasal symptoms for around 70% of those affected [25].

Eye symptoms are very common and distressing for those with nasal allergies. Over half of nasal allergy sufferers in the Allergies in America survey said that watery and red/itchy eyes bothered them a moderate amount or more. For 15% of sufferers, the eye part of allergic oversensitive reactions bothered them the most. Those with seasonal allergic conjunctivitis (SAC) had a notably lower quality of life score based on the Rhino-conjunctivitis Quality of Life Questionnaire (RQLQ) [26]. They also scored significantly less on various parts of the Visual Functioning Questionnaire 25 (VQF-25), including mental health, and social functioning. As healthcare becomes more global, the specific diagnosis of ocular allergy may be obscured by symptoms and descriptions. This is often evident in the literature where ocular allergy is frequently grouped under rhinoconjunctivitis. Additionally, cultural and language barriers, such as the Chinese term ‘Hot Qi’ used by parents in Hong Kong, may contribute to misinterpretation, suggesting an inflammatory process like infection or allergy [27].

While eczema in babies is usually a sign of their amazing sensitive skin, lots of kiddos see it clear up as they grow only to develop other super cool allergies like hay fever or asthma. Researchers tracked how a group of eczema cases turned out naturally and discovered that as the rash vanished for almost two-thirds of the group (60.5%), asthma showed up (34%). Sniffly, itchy eyes appeared (58%) - so their bodies were still finding new ways to react. It's so fascinating to see how these things can change as we develop [28].

So, the researchers were looking at eye and nose symptoms in people with asthma related to their jobs or workplace exposures. In one study, they found that eye itching, redness, and tearing were more common in people exposed to larger protein molecules on the job [29].

The Portugal Eye Allergy Study (PEAS) found some real doozies, folks. One in four folks had the watery eyes and sneezes more than five times in the past year - talk about never catching a break! Even worse, three in five said their eyes were hayfever factories all year round. No wonder they were grumpy, what with the constant allergic rhinitis (fancy word for sniffles) plaguing nearly half and asthma attacks hitting nearly one in six. True to form, the Portuguese were trying every home remedy before calling a professional. Only one in five made a doc appointment first thing, with over half trying their own sneeze cures. And get this - just over one in three had ever seen an allergy specialist before [30].

Figure 4 Prevalence of allergic conjunctivitis. The figure illustrates the distribution and prevalence of allergic conjunctivitis across different populations, demonstrating its high occurrence worldwide. Allergic conjunctivitis is shown to affect a substantial proportion of individuals, particularly in regions with increased exposure to environmental allergens such as pollen, dust, and air pollutants [31]. The prevalence is notably higher among children and young adults and is often associated with a personal or family history of

atopy, including allergic rhinitis and asthma. Seasonal variations are evident, with increased incidence during periods of high allergen load. The figure highlights allergic conjunctivitis as a common ocular condition with significant public health relevance, emphasizing the need for effective preventive strategies and appropriate therapeutic interventions [32].

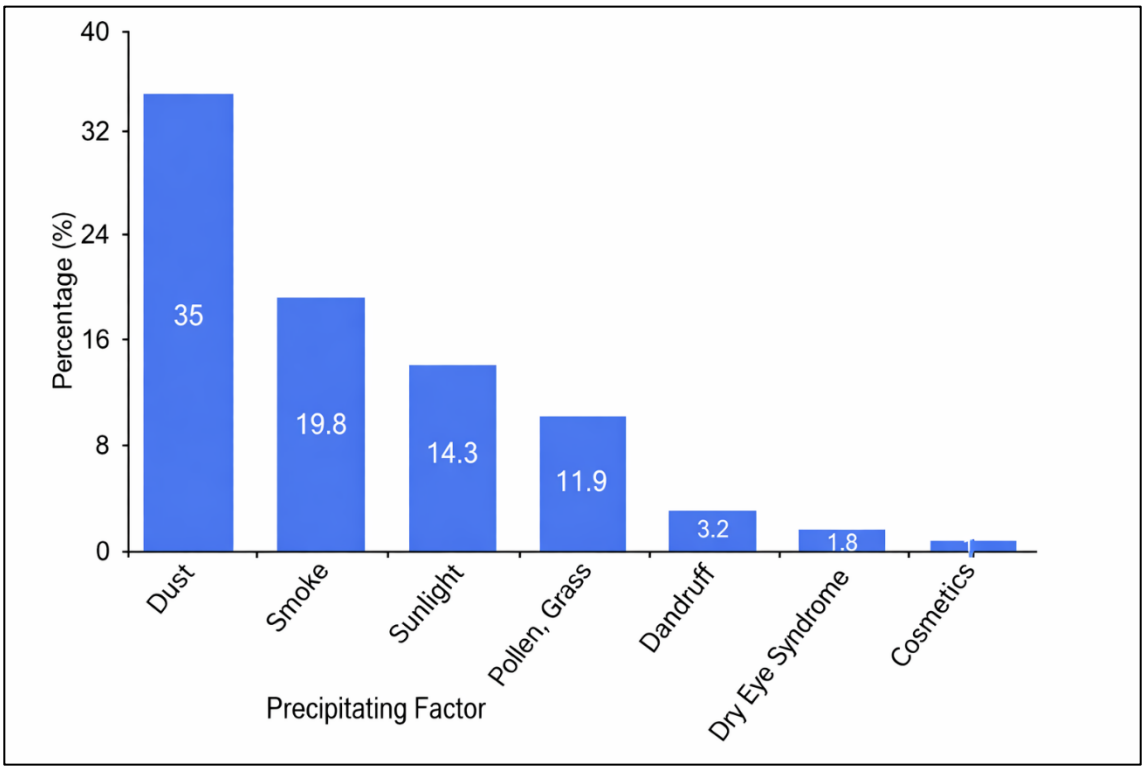

Figure 4: Prevalence of allergic conjunctivitis.

4. Pathophysiology

The ocular mucosa boasts an extensive surface area, making it exceptionally accessible for the direct deposition of antigens, thereby initiating the allergic cascade. Among ocular diseases, allergic conjunctivitis (AC) stands out as the only condition exclusively involving a type I allergic reaction [33]. So basically, in people who are allergic or sensitive to certain things, their Th2 cells release some chemicals called cytokines that cause B cells to start producing immunoglobulin E, which is also known as IgE. These IgE molecules then attach themselves to mast cells. When the allergen is present again and connects to the IgE, it triggers the mast cells to degranulate or release their contents. This includes histamine and tryptase that were already preformed inside the cells. It also causes the mast cells to produce some other chemicals like leukotrienes and prostaglandins. All of these substances then cause the typical allergic symptoms we see [34].

So allergic reactions happen in two phases. The early phase starts within minutes of exposure. During this time, mast cells release chemicals that cause symptoms like itching, tearing, redness, and swelling of the eyes. This early phase usually lasts 20-30 minutes. A few hours later, the late phase kicks in. This is when inflammatory cells like neutrophils, lymphocytes, basophils and eosinophils start infiltrating the eye tissue. This leads to prolonged inflammation and persistent symptoms. It also increases the risk of damaging the eyes. As the reaction continues, extra tears are produced. This drainage washes allergens from the eyes into the nasal passages through the tear ducts. So allergies that start in the eyes can end up affecting the nose as well [34, 35].

Figure 5 Immunopathogenesis of allergic conjunctivitis. The figure illustrates the cellular and molecular mechanisms involved in the development of allergic conjunctivitis following exposure to environmental allergens. Allergens penetrate the ocular surface and are processed by antigen-presenting cells, including macrophages and dendritic cells, which activate $CD4^+$ T cells and promote T helper 2 cell differentiation. These cells stimulate B lymphocytes to produce allergen-specific immunoglobulin E, which binds to mast cells. Upon re-exposure to the allergen, cross-linking of IgE on mast cells leads to rapid degranulation and release of inflammatory mediators [36]. This early phase reaction, occurring within minutes, results in mucosal edema and hypersecretion, manifesting as acute conjunctivitis. The late phase response, developing several hours later, is characterized by infiltration of inflammatory cells and sustained mediator release, contributing to chronic conjunctivitis. The combined effects of early and late phase responses lead to ocular symptoms such as itching, redness, sneezing, and nasal obstruction, highlighting the progression from acute to chronic allergic conjunctival inflammation [37].

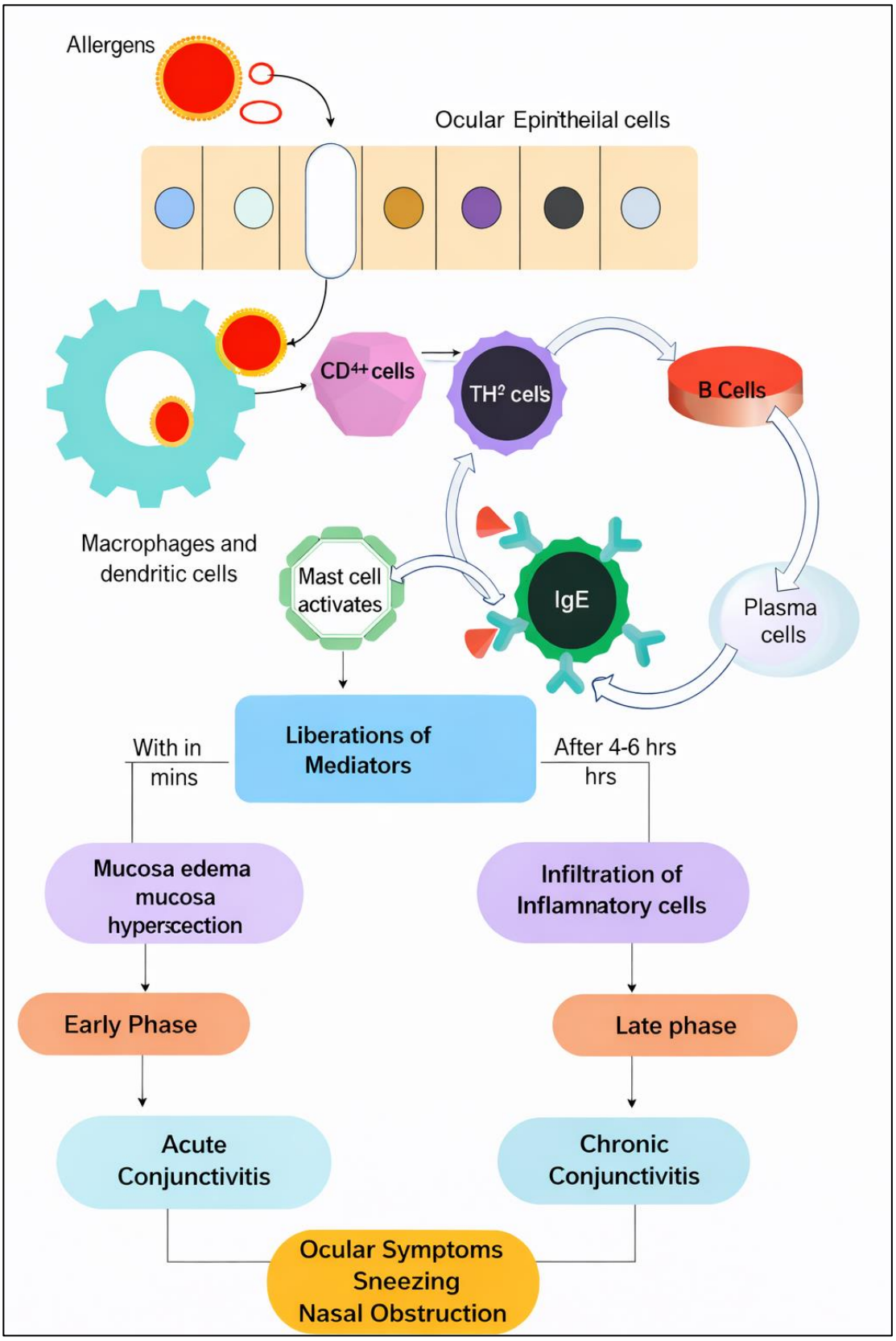

Figure 5: Scehmatic Pathophisiology of allergic conjunctivitis.

4.1 Detailed Pathology of Allergic Conjunctivitis

Over the past three years, meaningful progress has been achieved in understanding the disease mechanisms of allergic conjunctivitis. These insights have been gained through a meticulous evaluation of patient materials, such as conjunctival biopsy samples from individuals with both seasonal and persistent eye allergies, as well as analysis of enhanced murine models of ocular allergy. Through diligent research efforts, the field has moved closer to developing improved diagnostic tests and more targeted clinical interventions for this common ocular condition. Additional investigation will help translate recent basic science advances into enhanced care for allergic conjunctivitis. A novel those suffering from avenue of

exploration has focused on the genetic aspects of ocular allergy. The responsiveness of various mouse strains to specific allergen challenges in the eye has long been recognized, and ongoing linkage analyses of these mice aim to identify genes associated with susceptibility to ocular allergy [38].

Therefore, the adjustment of IL-10 production at the site of occurrence could potentially serve as a novel approach to treating ocular allergy, specifically linked to Seasonal Allergic Conjunctivitis (SAC). Ongoing genome-wide analyses for Vernal Keratoconjunctivitis (VKC) are in the final stages, and it is anticipated that these findings will identify unique gene products associated with the disease, offering potential avenues for the development of new drugs [39, 40].

Vernal Corneal inflammation (VKC) patients' conjunctiva have been discovered determined to consist of mixed TH1 (Th and TH2 cells, which were identified by inspection of conjunctival epithelium. Furthermore, it was recently established that those suffering with VKC and Seasonal Allergic The condition known as con (SAC) have tears consisting of the two beta-chemokines along with TH2-associated mediators. To adequately learn about the pathogenetic purpose of TH cells throughout VKC, additional study must be conducted. The investigation is projected to be made easier using the separate collection of T-cell lines from VKC sufferers, spotlighting the relevance of sorting out the resemblance of immune cells colonizing the membrane of the conjunctiva and realizing the physiological functions of various T-cell subsets in the disorder. There's more focus now on the cells in the lining of the eye, especially how allergens might activate them early on in causing problems. The T cells seen in the lining of eyes from people with VKC could play a role by changing the number or kind of cells there [41].

So, studies on human and mouse eyes have found that the cells that present antigens in the conjunctiva are a bit unusual. Specifically, there seem to be very few of the dendritic cells involved in the lymphatic system. On top of that, types of dendritic cells change a lot in eyes that are sensitive to allergies. This suggests there may be ways to modulate the immune system. Tests in mice with allergic eye issues have had success using an IL-1 receptor blocker. This success underscores how important dendritic cells and other local antigen presenting cells are in causing allergic conjunctivitis. So managing those cells may be a good way to treat allergic eye issues [42].

So, mast cell degranulation, which has been identified in biopsies from patients with SAC or VKC and mouse models, continues to be a major focus of research. It's really important that we understand how conjunctival mast cells develop and get activated. Studies using mast cell deficient mice and mice missing certain chemokine genes have revealed some unique pathways for priming and activating conjunctival mast cells. They highlight the role that beta-chemokines play in late-phase reactions and mast cell priming. Genetic analyses and direct examinations of human and mouse tissues implicate chemokines in causing ocular allergies. This suggests that blocking chemokines may help treat conditions. Similar studies are ongoing for blocking CCR1 as well. Researchers are currently investigating the potential effects of antagonizing the GPCR-CRTH2 receptor on early- and late-phase inflammation associated with ocular allergy. In conclusion, significant advances have been made in elucidating the clinical characteristics and molecular underpinnings of allergic conjunctivitis. Current work is focused on designing new treatment approaches utilizing existing pharmaceuticals and identifying novel biological targets suitable for rational drug development. Promising targets have been recognized, and preclinical studies are ongoing, indicating that a new generation of ocular anti-inflammatory medications may soon be available [43].

It is crucial to look into and determine which allergens the patient is allergic to because treating allergic conjunctivitis frequently requires documentation of an allergy. To identify the allergens causing the reaction, a thorough anamnesis is the first step. No further testing is required if the reason is well established [44].

Skin prick or patch testing is the next step if more research is required, even if no identifiable allergies have been discovered. For CBC, patch tests are the preferred method; for other illnesses, skin prick tests are employed. In addition to the conventional battery of allergens, these tests occasionally include additional allergens that are not often evaluated but are thought to be the source of the allergy. When skin testing is necessary but not advised. When systemic allergy evaluation tests yield conflicting results, a conjunctival allergen provocation test (CAPT) might help determine the cause [44, 45].

5. Confirmatory Test

5.1 Skin-prick test

Skin prick tests, also known as intradermal tests, are still one of the easiest and quickest ways to figure out what allergens may be causing issues for patients with eye allergies. These skin tests only take about 20 minutes to show results after the allergens are placed on the skin. If you get a nice wheal and flare reaction, that's a sign that you're sensitive to that specific allergen. The test does a really good job of detecting allergies that affect the whole body, like seasonal allergies or asthma. But it doesn't always correlate exactly with what may be causing problems on the eye surface. So, the skin test is mostly a confirmation tool. In rare cases, the doctor may want to do some other local tests directly on the eye [46].

When it comes to allergies, it's important to consider all types of tests. Skin prick tests can sometimes give different results than what's in the medical records. Sometimes a skin test just isn't a good option due to someone's health. That's where blood tests for specific IgE antibodies come in handy. Testing blood can help quantify just how much IgE someone has against certain allergens. Doctors may check both local allergens where you live, or even check very purified versions of things to pinpoint what's causing a

reaction. The bottom line, looking at both skin and blood tests together usually gives doctors the clearest picture of what might be triggering allergy symptoms [47].

5.2 Patch test

The existence of eyelid inflammation or eyelid-eye inflammation may also recommend the chance of an overdue kind and patch testing can be essential to recognize the unique antigen. It includes the use of a collection of potential chemical sensitizers in aluminum. those are removed after forty-eight hours and the patches examined at some time factors. Benzalkonium chloride and thimerosal, preservatives located in eye and touch lens solutions, are common culprits that can cause reactions. Patch testing allows the identification of what exactly causes the immune response in the eyes and skin. Thimerosal is a mercurial compound derived from the salicylic acid. It has been used as a disinfectant by binding to protein sulfhydryl groups, precipitating bacterial proteins to form mercurial proteinates. These proteinates act as neoantigens triggering an immune response, making thimerosal one of the most immunogenic ophthalmic preservatives. The skin around the eye is different from other areas like the back in terms of epithelial and dermal thickness and mast cell concentration. It also has less environmental exposure compared to eyelid skin. For example, sun exposure may exacerbate specific and non-specific hypersensitivity only on eyelid skin [48].

5.3 Conjunctival Provocation Test (CPT) or Conjunctival Allergen Challenge (CAC)

CPT or CAC can be compared to a "skin patch test" for the eye as small, measured amounts of specific allergens are placed on the eye's surface and the resulting allergic reaction is measured at 15-30 minutes similar to a skin test. eye's surface [49, 50]. So basically, when you do that eye drops allergy test, called the CPT, the immediate reaction is pretty much the same as what patients normally experience when exposed to whatever they're allergic to naturally. You'll get redness, and swelling of the lids, and the eyes will produce tears and itch. Usually, this initial response starts to improve within about 20 minutes. Sometimes there can also be a later phase reaction too, depending on how much of the allergen they used and how sensitive the patient is. But overall, it's considered a safe and easy way for doctors to get useful medical information with limited unwanted side effects like generalized itching, wheezing, or potentially life-threatening allergic reactions. Those severe issues don't happen very often with this eye drop allergy test [44].

5.4 Non-specific provocation test

It's been confirmed that people with allergies have a heightened sensitivity to the conjunctiva when exposed to certain things. Researchers were able to identify this by doing eye tests using histamine or hyperosmolar (overly concentrated) solutions on people. Lower levels of histamine were found to cause a reaction in individuals with a condition called vernal keratoconjunctivitis (VKC). While this is still considered a finding from research studies rather than a fact, it provides clues about the relationship between histamine and VKC [51].

5.5 Tear Film Investigation

5.5.1 Evaluation of Total Immunoglobulin E in Tear Fluid

Because of the blood-tear barrier, normal values of IgE in tears are often very low, less than 2.5 kU/l (3197 ng/ml). The presence of detectable antibody levels suggests the diagnosis of allergic conjunctivitis by indicating the local generation of antibodies [52].

5.5.2 Tear Osmolarity

To confirm the diagnosis of tear film dysfunction—formerly known as dry eye syndrome tear osmolarity should be assessed. Hyperosmolarity 31, 32, points to a type of dry eye [53].

5.6 Conjunctival Cytodiagnosis

Evaluating the types and percentages of white blood cells on the eye's surface during the active phase of a conjunctival infection can be important for deciding the next steps. Finding even one eosinophil strongly suggests an allergic cause, while their absence does not rule out allergy. Conjunctival scrapings using a spatula allow the collection of more cells than tear cytology using a glass capillary from the outer corner of the eye [54]. Conjunctival cytology is a technique for collecting cells from the lower eyelid for examination. This minimally invasive method allows clinicians to efficiently evaluate multiple inflammatory markers from conjunctival samples. The simple brushing technique provides valuable clinical information while minimizing discomfort for the patient. Conjunctival cytology offers ophthalmologists an effective diagnostic tool for assessing ocular inflammatory conditions [55].

6. Treatment

Despite the disruptive impact of allergic conjunctivitis on work, daily activities, and quality of life, a significant proportion of patients, approximately one-third, remain undiagnosed and untreated [45]. This oversight is concerning, especially given the escalating prevalence of allergic diseases, leading to increased effects on productivity and health-related costs. Consequently, there is a growing focus on research and clinical trials in this area [45, 56].

While effective treatments now exist for acute forms of ocular allergy, addressing perennial forms remains a subject of controversy [47].

6.1 Avoid Contact with Allergens

As an initial attempt, topical treatments should always be accompanied by nonpharmacologic [57] therapy. The optimum course of action is complete allergen avoidance, but this is often difficult to implement and is particularly crucial in PAC and SAC, as well as in VKC or AKC when a proven allergy is present. It is a problem in GPC as well, the symptoms of which can be lessened by switching to a different type of contact lens for the patient, temporarily stopping the wear of the lenses for shorter periods, or altering the cleaning solution. Daily disposable contact lenses are

particularly helpful in this regard [58]. Mechanical barrier gels for punctual occlusion have the potential to reduce allergic rhinoconjunctivitis symptoms and aid in the treatment of non-specific variables that exacerbate symptoms [59].

6.2 Non-pharmacologic Treatment

Particularly in cases of acute allergic conjunctivitis, cold, salt, water, and are helpful because they reduce symptoms and dilute allergens [45]. Recent research shows that topical medications that are used in conjunction with artificial [47].

6.3 Topical Vasoconstrictors/Decongestants

Among the earliest topical medications licensed for the treatment of allergy symptomatology were alpha-adrenergic agonists, particularly those that bind to Alpha-1 receptors, such as naphazoline [44]. Although they can be purchased over-the-counter and are used to treat hyperemia, it is not advised to use them on children or adolescents. They can be used for episodic itching and redness and have a quick onset of action, although patients may use them inappropriately. Six They have several side effects, including tachyphylaxis, eye irritation, and hypersensitivity, and a brief half-life. They are rarely recommended in our practice and should only be used as a temporary fix [47].

6.4 Antihistamines

There are numerous antihistamine drugs available on the market that can be used topically, but none have demonstrated a definite advantage over the others[60]. Levoca-bastine, pheniramine maleate, and azelastine are the most commonly utilized. For allergic rhino-conjunctivitis, oral antihistamines like loratadine, desloratadine, and fexofenadine work well. However compared to topical antihistamines, they are more likely to cause systemic adverse effects like drowsiness. They also result in fewer tears being produced, which may make conjunctivitis symptoms worse by causing dry eye symptoms[47].

Cetirizine and bilastine, two of the strongest antihistamines that are given systemically, have also been converted. Eight combinations of antihistamines and naturally occurring compounds with anti-inflammatory and antioxidant qualities (like catechin) as well as compounds with prolonged release (like cyclodextrin) have been proposed. For, drug-loaded contact lenses have been developed. These lenses may function as a sustained-release delivery system in addition to an allergen barrier, making them more effective than eyedrops[12, 47].

6.5 Mast Cell Stabilizers

They have a time of about 14 days and are utilized as prophylaxis because they prevent mast cell degranulation. Cromolyn sodium was the first medication of this kind to be created; more potent and acting more quickly were created later on [44].

6.8 Dual Action Agents

Topical dual-activity medicines are therapeutically superior in terms of both tolerability and symptom alleviation when compared to antihistamines. So some drugs can help with allergic eye issues. They work in a couple of different ways. Some stabilize mast cells to prevent them from degranulating and causing a reaction in the first place. Others block histamine receptors to stop the itch and inflammation once it starts [61].

A few names you may recognize are olopatadine, bepotastine, epinastine, azelastine, and ketotifen. The others are good for itch relief specifically. Now from what I've read, alcaftadine seems to be the best at stopping ocular itch or itching of the eyes. But some studies show olopatadine is both safe and effective, and may work better than ketotifen for clinical results. So, in the end, talking to your doctor is always a good idea to see which of these might be the best option based on your situation and symptoms [62].

6.9 Steroids: Topical ophthalmic and nasal

Steroids are used to treat allergic conjunctivitis (AC) by reducing the production of inflammatory cytokines, limiting mast cell growth, and modifying cell-mediated immune responses [63].

In severe clinical presentations of allergic conjunctivitis, ophthalmic steroids are often prescribed along with dual-action agents. They may also be used briefly to manage exacerbations or in times of expected high allergen exposure. Loteprednol etabonate 0.2% (Alrex® 0.2%) is preferred for treating anterior chamber inflammation and is more efficiently metabolized, reducing adverse effect risk. The 2% concentration is indicated for seasonal allergic conjunctivitis, with long-term use showing a minimal 1% incidence of significant intraocular pressure rise over 10 mmHg and no correlation with cataract development [64].

For severe AC, strong steroid creams like prednisolone acetate 1% (Pred Forte) and dexamethasone 0.1% may be prescribed. However, these stronger creams carry a higher risk of eye side effects and are usually not needed [65].

6.10 Topical NSAIDs

Eye drops that reduce inflammation usually aren't the first choice for treating itchy, red eyes caused by allergies. But they can help if other medications aren't working or if steroids aren't a good option for that person. These drops work by blocking one of the pathways that leads to inflammation. That pathway produces prostaglandins, which are substances formed during allergic reactions that cause more inflammation. The main benefit of eye drops containing anti-inflammatory meds seems to be temporarily relieving uncomfortable symptoms. So if other treatments aren't providing relief or aren't appropriate, anti-inflammatory drops may help calm things down [66]. Some are used in ocular allergies include ketorolac tromethamine in 0.4% and nepafenac in 0.1% (Nevanac®, Novartis) [67].

NSAIDs are commonly used after eye surgery to reduce swelling and inflammation. Doctors discovered they also help with seasonal allergic conjunctivitis

symptoms. Health Canada only approves eye NSAIDs for surgery recovery, but some are also used for seasonal allergies off-label. One NSAID called Ketorolac was specifically approved by the FDA for seasonal allergies. NSAIDs are generally used short-term along with other eye drops. Studies show using an NSAID four times a day for a week reduces eye itching, swelling, tearing, and redness. Side effects can include eye irritation. Rarely, they may cause corneal issues [67].

6.11 Immunotherapy

Immunotherapy stands out as the sole treatment capable of delivering sustained benefits even after the completion of an adequate course, so in summary, probiotics cause some adjustments to the immune system. They decrease the response involving Th2 cells. At the same time, they increase the activity of regulatory T cells. These regulatory cells make cytokines that put the brakes on inflammation. The result is that the body's reaction to allergens it comes into contact with is lowered. The immune system fights less when exposed to things it would normally see as threats, like pollen or pet dander. So, probiotics help create a calmer immune response and less allergy symptoms [68]. Two types of allergy shots are used in Canada [69].

6.11.1 Subcutaneous Immunotherapy (SCIT)

It's a type of immunotherapy treatment that in 1911. The goal is to help with symptoms from things like pollen or pet allergies. A lot of doctors recommend it for allergic rhinitis, which is when you get sneezing, stuffy nose, and all that fun stuff from allergies. It can take a few years of doing treatments, usually 3 to 5 years, but it seems to help people get long-lasting relief from their allergies if they stick with it for that long. Anyway, I hope this helps give you a brief overview of what SCIT is and how it can help treat environmental allergies. Pre-seasonal injections are available for three common allergens - trees, ragweed, and grass - while year-round therapy addresses a wider range of frequent triggers. Fourteen agents used to treat allergic rhino-conjunctivitis have been standardized, including extracts for cats, grass, pollen, house dust mites, and short ragweed [70].

6.11.2. Sublingual Immunotherapy (SLIT)

Opening, the most current frame of immunotherapy, can be conveyed as dissolvable tablets or extricate arrangement. In Canada, as it were tablets, such as Oralair® (Stallergenes Greer), and Grastek® are accessible. SLIT's viability was at first detailed for rhinitis, with its impacts on conjunctivitis investigated afterward. This analysis involving 13 randomized controlled trials and 1592 patients surveyed SLIT's effect on unfavorably susceptible rhino-conjunctivitis, counting reactions to different allergens. Opening successfully progressed adding up to visual indication scores and diminished visual redness, tingle, and tearing for pollen-induced AC, with a slant favoring tablets over drops Another meta-analysis covering 42 RCTs with 3958 patients showed a critical diminishment in adding up to visual side effect scores and visual signs for pollen-induced AC in both pediatric and grown-up populaces [71].

6.12 Biologics

A humanized monoclonal counteracting agent called omalizumab connects itself to the FCεR3 locale of unbound IgE. Omalizumab's impacts on AC have been reported in two RCTs that compared the medicine to a fake treatment [72]. So basically, after 12 and 16 weeks they noticed a pretty big drop in runny nose and eye symptoms like watery, red, and itchy eyes for the people taking omalizumab compared to those on the placebo. The use of omalizumab for treating allergic conjunctivitis specifically hasn't been looked at outside of studies on seasonal allergies. There have been some individual case reports though showing it can work well for conditions like vernal keratoconjunctivitis and atopic keratoconjunctivitis which involve eye inflammation and itching from allergies (AKC) [73].

7. Physical Examinations

Assessment of symptomatic patients ought to envelop an exhaustive examination. We propose utilizing bio-microscopy to scrutinize visual tissues, with a specific evaluation of the cornea and limbus, particularly in cases of direct and serious malady. All things considered, all patients, in any case of infection seriousness, can benefit from a comprehensive examination.

Bio-microscopy involves the assessment of different visual components, counting covers, lashes, top edges, Meibomian organs, tear film (counting release), bulbar and palpebral conjunctiva [36, 66]. In case accessible, fluorescein visual surface recolouring [74, 75].

Patients with unfavorably susceptible conjunctivitis (AC) may show unremarkable physical discoveries amid schedule perception, particularly exterior of exacerbations. Eyelids may appear as hyperemia and edema. An unfavorably susceptible "shiner," may be apparent amid intense illness due to venous blockage. For patients with allergic conjunctivitis, their physical exam may look pretty normal even during a routine checkup, especially when they're not in the middle of a flare-up. The eyelids could appear red and swollen, more so on the lower eyelid since gravity pulls things down there. During a severe episode, they may have what looks like a bruise under the eyes, which is a bluish discoloration from blocked veins. It gives them a bit of a tired look. But other than that, things look fine most of the time for allergic conjunctivitis patients [76].

8. Potential future paths for topical treatments

Looking ahead to the future of topical treatments for allergic conjunctivitis (AC), it is evident that topical steroids have demonstrated success in managing the condition. Ester-based steroids, with their lower risk of Adverse effects such as elevated cataract formation, have proven effective. Notably, ongoing clinical trials are exploring experimental ocular models, Mapracorat has shown the ability to reduce eosinophil recruitment and cytokine production, with the added advantage of causing less IOP elevation compared to the topical steroid dexamethasone [77].

8.1 Allergen desensitization

Asthma and allergic rhinitis are currently treated with subcutaneous allergen desensitization. It has been demonstrated to lessen rhino-conjunctivitis symptoms [78]. SLIT is a method of desensitization that uses grass-allergen pills. The research has proven to be both safe and efficient in treating allergic rhinitis. It did not demonstrate a decrease in the usage of topical ophthalmic drugs, but it did find that SLIT was beneficial in lowering ocular discomfort. Currently, a Phase III trial focusing on allergic rhinitis with or without is being conducted using Merck's investigational SLIT, MK-8237. To establish the ideal dosage and clarify the function of SLIT in the management of allergic conjunctivitis, more investigation is required [79].

8.2 Selective glucocorticoid receptor agonists

Specific glucocorticoid receptor agonists (SEGRAs) are a generally unused restorative alternative right now beneath advancement. As already expressed, the delayed utilization of topical corticosteroids can lead to extreme side impacts. Be that as it may, transactivation has been related to more antagonistic impacts. This instrument shows up to trigger the aggregation of extracellular fabric within the outpouring channels of the trabecular meshwork, possibly causing an increment in intraocular weight (IOP) due to corticosteroid utilization. Specific glucocorticoid receptor agonists have been particularly planned to target these instruments and possibly minimize hurtful side impacts [80].

8.3 Toll-like Receptors

It has been demonstrated that corneal and conjunctival cells have toll-like receptors (TLRs), which are being researched as potential targets for novel drugs**.** The anti-allergic properties of substances that repress the TLR signal framework, such as opponents or receptor adversaries, are examined. A vitamin D receptor ligand, a quinazoline subordinate, antihistamines, leukotriene adversaries, pole cell stabilizers, anti-IgE drugs, pyrimidine subordinates, oligo-deoxy-nucleosides, and TLR antibodies are a few of these substances. The foundation of an eosinophil-driven last-phase response shows up to be subordinate to TLR3 on visual surface epithelial cells in particular [81].

8.4 Other Potential Targets

Some targets are under examination for eye conditions. Spleen tyrosine kinase has been illustrated to play a portion in eosinophil enlistment, pole cell degranulation, and cytokine era, proposing a potential work in sensitivity [82]. Cyclosporine A, known for its capacity to smother T lymphocyte expansion and provocative cytokine movement, has appeared to guarantee to lessen the unfavorably susceptible reaction by repressing histamine discharge from pole cells and basophils and diminishing eosinophil enrolment [83]. An efficient audit proposes that topical cyclosporine may be a reasonable alternative for treating AC, possibly lessening the dependence on topical steroids, especially in more serious cases. Even though regarded as secure, with detailed side impacts being burning and stinging upon ingrained, advanced considerations are required to decide the suitable concentration of cyclosporine for different sorts and severities of AC [84].

Conclusion

At last, I wanted to discuss some options for treating certain eye conditions. While medications like tacrolimus and pimecrolimus have been shown to work well for skin issues like eczema, they aren't approved for use in the eyes yet. However, researchers in Japan had some success using very low-dose tacrolimus eye drops to treat a condition called atopic keratoconjunctivitis, or AKC, including in people who didn't get better with cyclosporine drops. The tacrolimus seemed to help even when cyclosporine didn't work. Of course, long-term use of tacrolimus has a potential link to cancer risk, so more research is still needed in this area to make sure it's a safe treatment option for eye problems. Overall, it's promising, but they want to study it further before recommending it widely.

Acknowledgment

The authors sincerely acknowledge their respective institutions for providing the necessary facilities and academic support to carry out this review work. The authors are also grateful to colleagues and peers for their constructive suggestions during the preparation of the manuscript.

Author Contribution

MS; Literature survey, **RK**; Conceptualization of the review, **SK**; Manuscript drafting.

Source of Funding

None

Ethical Approval

Not applicable

Data Availability

All data provided in the manuscript are original.

Conflicts of Interest

There are no conflicts of interest

Declarations

The authors declare that they used AI language tools (ChatGPT and Grammarly Premium) to enhance this manuscript's linguistic clarity and readability. They carefully reviewed and edited all generated text to ensure accuracy and alignment with the research's intended meaning.

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