IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

PERSPECTIVES OF ALLERGY

[1]Arundhuti Chatterjee, [2]Shwet Nisha, [3]Moutusi Nath, [4*]Gargi Sen

[1]Post Graduate Scholar, [2]Post Graduate Scholar, [3]Assistant Professor, [4]Associate Professor
[1-4]Department Of Optometry,
[1-4]NSHM College Of Management And Technology, Kolkata, India
*Address for Correspondence: Dr.Gargi Sen, Associate Professor, Department of Optometry & Vision Science, NSHM College of Management & Technology, Kolkata, India Tel: 8910323015; Email: gargi.sen@nshm.com

Abstract: Ocular allergy represents one of the most common conditions encountered by optometrists in their clinics. Allergic conjunctivitis is often underappreciated and undertreated. It is rarely vision threatening but can significantly decrease the quality of life for patients. In India, a large number of urban population is deemed to be affected and this number was growing in pre-covid era. The vast increase in ocular allergy in clinics has been attributed to enhanced pollution level in the cities. An attempt was made to review this relatively less explored topic through multidisciplinary collaborations. This review provides a summary of the forms of ocular allergies, with a focus on symptoms and signs, impact on quality of life and therapeutic options of allergic conjunctivitis.

Index Terms **– Allergy, Pollution, Immunotherapy.**

I. INTRODUCTION

Allergic Conjunctivitis is often observed in patients with other allergic conditions such as allergic rhinitis and asthma. This resulted in less study on the prevalence of the disease Although reports suggest that this disease has an increasing trend in the last decade particularly in urban areas and during certain seasons there is paucity of data from India. Allergic conjunctivitis is the ocular manifestation of allergy, where the immune system produces a hypersensitivity to normal harmless substances known as allergens. Ocular itching is a cardinal symptom of allergic conjunctivitis and in the absence of itching differential diagnosis should be made. This disease is associated with variable factors such as environment and lifestyle with delayed acquisition of Th1 function in childhood. Reduced microbial exposure in early life is responsible for a shift of Th1/Th2 balance in the immune system towards the pre-allergic Th2 response. Genetics play an important role in pathogenesis of the disease [1,2].
Environmental factors contributing to the disease include increased air pollution, climate change and increased planting and importation of allergenic plant species [3,4,5]. Of all those who suffer from allergy, approximately 15-20% experience a form of ocular allergy [6,7].
As Allergic conjunctivitis is often under-recognized both by patients and clinicians we attempted to provide the clinicians with a considerable understanding of the pathogenesis of allergic eye disease.

II. OCULAR ALLERGIES

Allergic eye disease encompasses a group of distinct clinical entities, typically confined to the conjunctiva, and includes allergic conjunctivitis which is subdivided into seasonal and perennial forms, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis(GPC) [8,9,10]. Giant papillary conjunctivitis occurs when one or several small round bumps (papillae) develop on the upper tarsal conjunctiva. Although not fully understood, VKC a severe inflammatory disease that appears in children and adolescents is considered a non-classic type-I IgE mediated, Th2-lymphocyte driven allergic disorder involving mast cells and eosinophils [11,12,13].
VKC can cause severe visual complications but appears mainly seasonally and is associated with a variety of factors, including environmental allergens, climate, and genetic predisposition. Mast cells and eosinophils and their mediators play major roles in the clinical manifestations of VKC. Trantas' dots and large cobblestone papillae are indicative of the condition. VKC can be differentiated from other allergic conditions through a comprehensive clinical history and ophthalmic examination.
Symptoms of AKC typically begin in the late teens or early twenties and can sometimes follow childhood VKC [12]. AKC is considered to be the ocular component of atopic dermatitis(AD), with 20-40% of AD patients suffering from AKC [14]. AKC is thus a severe ocular surface disease affecting some atopic individuals. The disease has complex immunopathology including T-cell mediated (type 4 hypersensitivity).
AKC is more common in males and often occurs between the ages of 18 to 40 years [11]. AKC is a chronic, potentially blinding, bilateral condition. Signs include giant papillary hypertrophy and scarring of the palpebral conjunctiva (typically superior), chemosis and diffuse conjunctival hyperaemia [11,15]. Limbal papillae may also occur and the eyelids of AKC patients are often thickened, erythematous, fissured and crusting, and blepharitis (chronic staphylococcal) may be present [11,15]. Symptoms include ocular itching, burning, watering (usually bilateral), blurred vision, photophobia, white stringy mucoid discharge. Onset of ocular symptoms may occur several years after onset of atopy. Symptoms usually occur round the year, with exacerbations.

Seasonal allergic conjunctivitis is the most common form of ocular allergy. Both seasonal and perennial allergic conjunctivitis are IgE-mediated, hypersensitivity and symptoms include ocular pruritus, epiphora, and hyperemia. Diagnosis is made clinically based on history and physical examination. Allergic conjunctivitis has been found to be frequently associated with allergic rhinitis [16]. Predisposing risk also include a history of atopy including eczema and asthma [16,17,18]. Seasonal allergic conjunctivitis occurs on a seasonal basis, often as part of seasonal rhinoconjunctivitis and hay fever which peak at certain times of the year [12,17]. Perennial allergic conjunctivitis occurs year round and is often due to presence of house dust mites, animal dander, insects and indoor moulds [12]. Although the symptoms of allergic conjunctivitis are relatively mild, the impact of the same on the quality of life can be profound [19], affecting daily activities, productivity at work, school performance and has impact on economy of the patient [20,21,22]. Significantly reduced quality of life has been found to be associated with acute episodes of allergic conjunctivitis [22]. As there is no permanent cure for allergic conjunctivitis and clinicians counsel the patients on preventive measures apart from providing them symptomatic relief.

III. AIR POLLUTION AND EYE PROBLEMS

Exposure to ambient air pollution increases morbidity and mortality and it's been a leading contributor to global disease burden since industrialization. Levels of toxic air pollution in urban areas are on the rise and the air the people are inhaling are laden with particulate matters and gaseous pollutants. The most common reasons for this increase in air pollution include open burning of agricultural waste, fumes of transport vehicles and industrial gaseous wastes. In 2017, the government had declared that pollution levels in many cities have reached a level of emergency, and has the potential of becoming a health hazard. The eyes are exposed to all the harmful chemicals in the environment. Extreme pollution in the form of smog affects the eyes, causing allergies and other damages. Compromised quality of air because of the presence of harmful matters have led to more number of people complaining of red and watery eyes and various eye allergies. Conjunctiva acts as a barrier as it is the outer layer of the eyes and protects our eyes from outside deleterious agents like air pollutants that tend to penetrate deeply and stay there for long period. The cleansing system of the ocular surface (tears) is capable of alleviating the cellular damage induced by air pollutants. As the ocular surface is directly exposed to the environment, it is more susceptible to weather changes. This importance of conjunctiva and a high prevalence of conjunctivitis merit more studies on air pollution as well as weather changes, associated with risk for allergic conjunctivitis. Some studies have found high prevalence of the severe forms of allergic conjunctivitis, including AKC and VKC, associated with the levels of the air pollutants like NO_2. The significant associations between the allergies and the levels of air pollutants call for need of clinicians to be aware that air pollutants that may pose serious risks of vision threatening severe ocular allergy. Changes in the lacrimal pH—caused by the acidification of tears exposed to a high-oxidant concentration (NO_2 and SO_2)— irritates the ocular surface. NO_2 and O_3 have high oxidative potential and are able to cause damage to ocular mucosa and may induce conjunctival inflammation.

IV. ALLERGENS

Allergens causing conjunctivitis are immunogens that tend to activate specific type of humoral or cell mediated response in eye [18]. The allergic reaction has two phases. When the patient comes into contact with an allergens, sensitised IgE antibodies trigger mast cell degranulation releasing histamine, cytokines, prostaglandins, thromboxanes, leukotrienes, and eosinophil chemotactic factors. Histamine then attaches to receptor sites causing irritation, inflammation and oedema. The influx of eosinophils in particular, provides additional inflammatory mediators and contributes to local injury [23,24] report suggest that grass pollens and rag weed pollens are especially irritating to the eyes of many patients. Even though people blink at an average of 15,000 times a day, pollen still enters the eyes. Pollen studies have elucidated the molecular and cellular pathways involved in initiating allergic conjunctivitis and have found threshold, linear increase and plateau point in relationship between pollen levels and conjunctivitis symptoms [25,26]. Steps that patients should be advised to take to reduce pollen's irritating effect on their eyes include washing frequently, using saline rinses or artificial tears, Wearing sunglasses, closing the windows , applying cold compress etc[27]. Pollination occur at all hours of the day or night, so people with hay fever and other allergies can use air filters at their homes to filter allergens.

V. GENETICS

The interplay of genetics and the environment in the pathological mechanism of allergic diseases has long been pointed out. However, most studies on the genetic basis of allergic disease have focused attention on other manifestations such as asthma, eczema and rhinitis and there is scope of studying the genetic basis of ocular allergies in future.[1,2] Hereditary studies indicate that atopic conditions frequently occur within families and that children born to allergic parents have an increased risk of developing an atopic condition in their lifetime. Acute allergic conjunctivitis has a strong hereditary tendency; and studies have pointed out at genetic association in atopic keratoconjunctivitis. However, certain aspects of the genetics of ocular allergy indicate peculiarities independent of other allergic diseases. The inheritance of ocular–allergic disease does not obey the classical Mendelian order, and follows complex inheritance pattern influenced by multiple factors. Numerous studies have shown that allergen recognition and antibody response are affected by the HLA-Linked genes; however, studies that attempted to investigate a similar link between HLA-Linked genes and ocular-allergic disease remained inconclusive.[28,29] Chromosomal studies through genetic mapping have indicated anomalies in the gene cluster encoding for cytokines, including IL-4, IL-13, IL-3, IL-5 on chromosome-5 and interferon-gamma, and these have implications for asthma and other atopic diseases.[30,31] Recent evidence suggests the involvement of chromosomes 5, 16 and 17 in allergic conjunctivitis, with additional weak linkage detected for chromosome 6 for specific allergens [32]. Many Scientists are of the opinion that the genetic linkage for allergic conjunctivitis differs from that reported for asthma and other atopic disorders. This is because organ-specific disease-susceptible genes, together with general atopy genes, may interact in the allergic response to specific mucosal tissues. The genetic correlation between ocular allergy, comorbidities and complications still remain to be explored.

VI. DRUGS FOR TREATMENT OF ALLERGIC CONJUNCTIVITIS

t should be noted that allergic diseases of the eye surface needs to be addressed by a multidisciplinary team mainly involving clinicians and allergists as ocular and systemic comorbidities needs to be promptly diagnosed and treated. Avoidance of allergens can be difficult to implement for aeroallergens but will improve the symptoms. Non-pharmacological measures, such as lubricants or artificial tears may be used to dilute the antigen load, increase the clearance of allergens on the eye surface and dilute the inflammatory mediators. To suppress the inflammation and symptoms of allergic conjunctivitis, drugs that target many points in the inflammatory reaction cascade might be necessary. Treatment may consist of mast cell stabilizers, dual mechanism anti-allergen agents or topical antihistamines. However these treatment has short duration of action. Leukotriene receptor antagonists that are currently available for oral dosing, prevent leukotrienes from binding to their conjunctival receptors to decrease inflammatory signalling and improve multiple ocular symptoms associated with ocular allergy. Oral antihistamines are often used for short term relief to itching of eye however long term use of the drug can lead to drying of the ocular surface, decreasing the barrier to allergens and the ability of the tear film to flush away allergens [33]. All topical NSAIDs (*e.g.*, ketorolac, nepafenac, bromfenac) used to reduce itching has short term effect. Treatment of the rarer and more severe forms of allergic conjunctivitis require the use of topical corticosteroids. However prolonged use of topical steroids in the eye can lead to secondary bacterial infection, intra-ocular hypertension, glaucoma and cataract, and thus regular monitoring of patients is highly essential. Topical cyclosporine eye drops are approved for use in the US for chronic dry eye syndrome, and is often used in patients with severe VKC and AKC .Patients who experience moderate to severe symptoms of allergic conjunctivitis require more effective and longer-lasting treatment. Immunotherapies have improved the lifestyle of patients but is relatively costly option of treatment when patients see the initial cost of treatment.[34] Reports suggest that immunotherapy can effectively reduce immune responses to seasonal or environmental allergens in patients and prevents the activation of inflammatory cascades and development of conjunctivitis.[34,35] However many patients do not complete the course of desensitizing immunotherapy because a long term treatment is required.

STATEMENT	MANAGEMENT
PATIENT HISTORY AND PHYSICAL EXAMINATION	Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause and 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing.
ALLERGY TESTING	Clinicians should perform and interpret, or refer to a clinician who can perform and interpret, specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy[36].
IMAGING	Clinicians should not routinely perform sinonasal imaging in patients presenting with symptoms consistent with a diagnosis of AR.[36]
CHRONIC CONDITIONS AND COMORBIDITIES	Clinicians should assess patients with a clinical diagnosis of AR for, and document in the medical record, the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media.[36]
ENVIRONMENTAL FACTORS	Clinicians may advise avoidance of known allergens or may advise environmental controls (eg, removal of pets; the use of air filtration systems, bed covers, and acaricides [chemical agents that kill dust mites]) in AR patients who have identified allergens that correlate with clinical symptoms.[36]
TOPICAL STEROIDS	Clinicians should recommend intranasal steroids for patients with a clinical diagnosis of AR whose symptoms affect their quality of life.[36]
ORAL ANTIHISTAMINES	Clinicians should recommend oral second-generation/less sedating antihistamines for patients with AR and primary complaints of sneezing and itching.[36]
COMBINATION THERAPY	Clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy.[36]
IMMUNOTHERAPY	Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.[36]

Table 1:- Management Guidelines

VII. DISCUSSION

From a public health perspective, the prevalence of allergic disorder is increasing on regular basis because of the environmental issues. Patients with blepharitis, eczema, keratoconjunctivitis sicca, and other types of conjunctivitis may occasionally present with ocular itching and so differential diagnosis for identification of allergic conjunctivitis is very important. Although not pathogenic, recurrent ocular itching disrupts the lifestyle of the patients decreasing their productivity and quality of life in most cases. Management of the disease is very challenging and needs multidisciplinary approach which involves optometrists, ophthalmologist, immunologist and allergy specialists. Dual acting Topical ocular antihistamine- mast cell stabilizer formulations are first-choice medications because these formulations rapidly alleviate allergic symptoms and reduce late-phase responses that occurs due to mast cell degranulation[37]. Long term therapeutic strategy for controlling ocular allergy is immunotherapy, a technique of hypo-sensitizating the immune system so that responses to common allergens such as pollen, animal dander, or dust mites gets attenuated.[35] Immunotherapy often leads to lasting relief of allergy symptoms even after treatment is stopped. This ultitmately makes it a cost-effective, beneficial treatment approach for many people. There are two phases in the treatment[38]. Firstly the build-up phase. which involves receiving injections with increasing amounts of the allergens about one to two times per week. This followed by maintenance phase. This begins once the effective dose is reached which depends on the level of allergen sensitivity and patients response to the build-up phase. During the maintenance phase, there will be longer periods of time between treatments.This treatment option has very few adverse effects. Recently, tablet-based sublingual allergy immunotherapy has been introduced in the treatment of allergic disorders . The treatment appears to be more patient-friendly concept.

VIII. ACKNOWLEDGEMENT

The authors would like to acknowledge support received from Director, School of Health Sciences, NSHM Knowledge campus for conducting this review. The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the aricle apart from those disclosed.

No writing assistance was utilized in the production of this article.

REFERENCE

[1]. Holloway J. W., Yang A. I., & Holgate S. T. (2010). Genetics of allergic disease. J Allergy Clin Immunol, 125(2 Suppl 2):S81-94.

[2]. Swarr D. T., Hakonarson H. (2010). Unraveling the complex genetic underpinnings of asthma and allergic disorders. Curr Opin Allergy Clin Immunol 10, 434-442.

[3]. Linneberg A., Jorgensen T., Nielsen N. H., Madsen F., Frolund L., Dirksen A. (2000). The prevalence of skin-test-positive allergic rhinitis in Danish adults: two cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. Allergy, 55(8): 767-72.

[4]. Alcázar P., Cariñanos P., De Castro C., Guerra F., Moreno C., Domínguez-Vilches E., & Galán C. (2004). Airbone plane-tree (Platanushispanica) pollen distribution in the city of Cordoba, South-western Spain, and possible implications on pollen allergy. Journal of Investigational Allergology and Clinical Immunology, 14, 238-243.

[5]. D'amato G., Cecchi L., Bonini S., Nunes C., Annesi-Maesano I., Behrendt H., Liccardi G., Popov T., & Van Cauwenberge P. (2007). Allergenic pollen and pollen allergy in Europe. Allergy, 62(9), 976-990.

[6]. Abelson M. B., Leonardi A., & Smith L. (2002a). The mechanisms, diagnosis and treatment of allergy. Review of Ophthalmology. 9(4); 74-84.

[7]. Leonardi R., Chohnan S., Zhang Y. M., Virga K. G., Lee R. E., Rock C. O., Jackowski S. (2005). A panthothenate kinase from Staphylococcus aureus refractory to feedback regulation by coenzyme A. J. Biol. Chem., 280: 3314-3322.

[8]. Abelson M. B., & Schaefer K. (1993). Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. Survey of Ophthalmology, 38, 115-132.

[9]. Friedlaender M. H. (1993). Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. Survey of Ophthalmology, 38, 105-114.

[10]. Bielory L. (2000). Allergic and immunologic disorders of the eye. Part II: Ocular allergy. Journal of Allergy and Clinical Immunology. 106(6); 1019-1032.

[11]. Bonini S., Coassin M., Aronni S., & Lambiase A. (2004). Vernal keratoconjunctivitis. Eye,18(4), 345-351.

[12]. Chigbu D. G. I. (2009a). The pathophysiology of ocular allergy: a review. Contact Lens and Anterior Eye, 32(1), 3-15.

[13]. Kumar S. (2009). Vernal keratoconjunctivitis: a major review. Acta Ophthalmologica, 87(2), 133-147.

[14]. Bielory B., & Bielory L. (2010). Atopic dermatitis and keratoconjunctivitis. Immunology and Allergy Clinics of North America, 30(3), 323-336.

[15]. Tuft S. J., Kemeny D. M., Dart J. K., & Buckley R. J. (1991). Clinical features of atopic keratoconjunctivitis. Ophthalmology, 98(2), 150.

[16]. Rosario N., & Bielory L. (2011). Epidemiology of allergic conjunctivitis. Current Opinion in Allergy and Clinical Immunology, 11(5), 471-476.

[17]. Bielory L. (2008a). Ocular allergy overview. Immunology and Allergy Clinics of North America. 28(1); 1-23

[18]. Leonardi C. L., Kimball A. B., Papp K. A., Yeilding N., Guzzo C., Wang Y. (2008). Efficacy and safety of ustekinumab, a human interleukin-12/13 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). FAST TRACK, 371, P1665-1674.

[19]. Bielory L. (2006). Allergic diseases of the eye. Med Clin North Am, 90(1):129-48.

[20]. Pitt A. D., Smith A. F., Lindsel, L., Voon L. W., Rose P. W., & Bron A. J. (2004). Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. NeuroOphthalmology, 11(1), 17-33.

[21]. Smith A. F., Pitt A. D., Rodruiguez A. E., Alio J. L., Marti N., Teus M., Guillen S., Battaille L., & Barnes J. R. (2005). The economic and quality of life impact of seasonal allergic conjunctivitis in a Spanish setting. Ophthalmic Epidemiology, 12(4), 233-242.

[22]. Palmares J., Delgado L., Cidade M., Quadrado M. J., & Filipe H. P. (2010). Allergic conjunctivitis: a national cross-sectional study of clinical characteristics and quality of life. European Journal of Ophthalmology, 20(2), 257.

[23]. Anderson D. F., Macleod J. D. A., Baddeley S. M., Bacon A. S., McGill J. I., Holgate S. T., Roche W. R. (2006). Seasonal allergic conjunctivitis is accompanied by increased mast cell numbers in the absence of leucocyte infiltration. Clinical & Experimental Allergy,27(9).

[24]. Kawasaki H., Nagao K., Kubo A., Hata T., Shimizu A., Mizuno H. (2012). Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. J Allergy Clin Immunol, 2012; 1538-1546.

[25]. Prince A., Norris M. R., Bielory L. (2018). Seasonal ocular allergy and pollen counts. Allergy and Clinical Immunology, 18(5): 387-392.

[26]. Kitinoja M. A., Hugg T. T., Siddika N., Yanez D. R., Jaakkola M. S., Jaakkola J. J. K. (2020). Short term exposure to pollen and the risk of allergic and asthmatic manifestations: a systematic review and meta-analysis. BMJ Open, 2020, 10;10(1):e029069.

[27]. Chan S. (2016). Pollen Allergy: Prevent Eye Irritation. National Jewish Health, 2016.

[28]. Jonathan H. A., Elizabeth P. J., Simon M. A., Peggy K. L. (2015). The Evolving Story of HLA and the Immunogenetics of Peanut Allergy. Ann Allergy Asthma Immunol, 2015;115(6): 471-476.

[29]. Mishra M. N., Dudeja P., Gupta R. K. (2014). Association of HLA-Class II and IgE serum levels in pediatric asthma. Iran Immunol, 2014;11(1):21-28.

[30]. Hani A. A., Ahmed A. A., Naief A., Zeiad A. A., Zafar R. (2016). Molecular Genetics of Atopic Dermatitis: An Update. Int J Health Sci (Qassim). 2016;10(1): 96-120.

[31]. Gutowska-Owsiak D., Schaupp A. L., Salimi M., Selvakumar T. A., McPherson T., Taylor S., et al. (2012). IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. Exp Dermatol,2012;21:104-10.

[32]. Akio N., Robert S. Campbell-Meltzer, Kathy C., Jeff O. (2001). Genetics of Allergic Disease: Evidence for Organ-Specific Susceptibility Genes. International Archives of Allergy and Immunology,2011;124(1-3):197-200.

[33]. Ousler G. W., Workman A., Torkildsen G. L. (2007). An open-label, investigator-marked, crossover study of the ocular drying effects of two antihistamines, topical epinastine and systemic loratadine, in adult volunteers with seasonal allergic conjunctivitis. J. Clinthera, 4,P611-616.

[34]. Arshad S. H. (2016). An update on allergen immunotherapy. Clin Med (Lond.), 2016;16(6): 584-587.

[35]. Adrian W. Y. Y. (2012). Immunotherapy – Vaccines for allergic diseases. J Thorac Dis, 2012;4(2): 198- 202.

[36]. Seidman M. D., Gurgel R. K., Y Lin S., Schwartz S. R., Baroody F. M., Bonner J. R., Dawson D. E., Dykewicz M. S., Hackell J. M., Han J. K., Ishman S. L., Krouse H. J., Malekzadeh S., Mims J. W. W., Omole S. F., Reddy W. D., Wallace D. V., Walse S. A., Warren B. E., Wilson M. N., Nnacheta L. C. (2015). Clinical practice guidelines: Allergic rhinitis. Otolaryngol Head Neck Surg,2015;152(1):S1-43.

[37]. Carr W., Schaeffer J., Donnenfeld E. (2016). Treating allergic conjunctivitis: A once-daily medication that provides 24-hour symptom relief. Allergy Rhinol (Providence),2016;7(2):e107-e114.

[38]. Pongdee T. ALLERGY SHOTS (IMMUNOTHERAPY). The American Academy of Allergy, Asthma & Immunology (AAAAI).