

# An overview of allergic conjunctivitis

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## Abstract

Allergic diseases affect many people across the globe. They significantly impact on the quality of life of the people who are affected, creating personal and economic predicaments. Some of the most commonly diagnosed allergic diseases include atopic dermatitis, rhinitis, allergic conjunctivitis and sinusitis. Allergic conjunctivitis is an allergic disease characterised by the inflammation of the conjunctiva caused by airborne allergens; it presents as itching, excessive lacrimation, discharge and pink eye. Usually it is associated with other allergic conditions such as allergic rhinitis and bronchial asthma. Allergic conjunctivitis is further divided into acute, seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC). Other conditions, such as eosinophilic oesophagitis, are on the rise and are being diagnosed across all continents except Africa. The diagnosis is primarily clinical. Antihistamines have been the mainstay of therapy for most allergic conditions, except for other conditions that require corticosteroids, or in severe allergic conditions such as anaphylaxis where antihistamines are ineffective as main therapy. It is important to consider first- versus second-generation options when treating allergic diseases, also bearing in mind the duration of therapy and any comorbid conditions that a patient might have. This article provides an overview of these conditions and their current management options.

**Keywords:** allergic disease, antihistamine, anaphylaxis, atopy, atopic march, rhinitis, sinusitis

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## Introduction

Allergic diseases are complex diseases caused by a combination of genetic and environmental factors. Allergic diseases are on the increase, affecting approximately 30% to 40% of the world's population. They decrease quality of life and may have an immense influence on personal, social, and economic costs.<sup>1</sup>

An allergic response is a hypersensitivity reaction mediated by the adaptive immune system. The presence of a trigger, such as an allergen or antigen, induces a humoral immunological response, which in turn initiates a complex immunological reaction. This dysregulation in the immune function elevates the plasma levels of immunoglobulin E (IgE). The release of IgE is followed by binding to the allergen or antigen, which in turn stimulates the mast cells to degranulate and release several pro-inflammatory substances that include histamine, chemokines and numerous cytokines.<sup>2</sup>

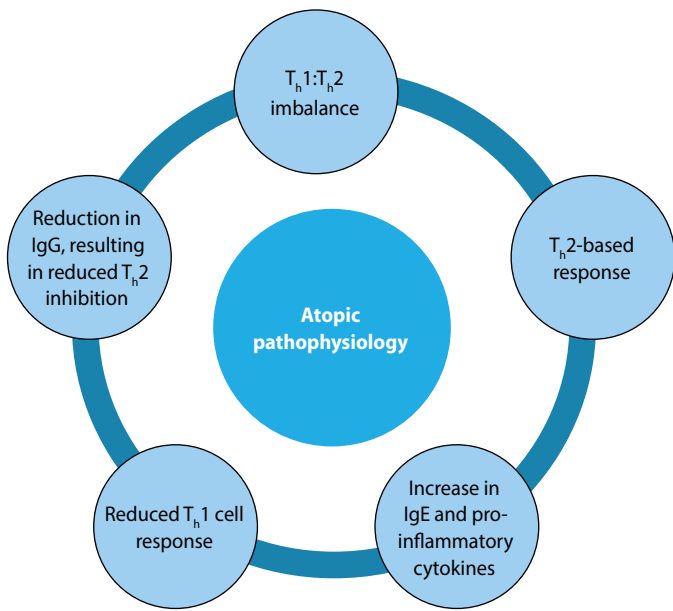
There are many different factors that come into play when searching for the causative agent of an allergy. Environmental influences that occur in pregnancy and early childhood can alter the physiological, immune, structural and behavioural development of an individual and thus, transform response patterns that influence susceptibility to future diseases.<sup>3</sup> Genetics also play a vital role in the susceptibility of an individual to an allergic disease. The most common allergic conditions around the world include atopic dermatitis, rhinitis, asthma, rhinosinusitis, allergic conjunctivitis and, most recently, allergic oesophagitis.<sup>3,4</sup> Allergic conjunctivitis is primarily a condition that affects young adults, with the average age of onset being 20 years. The symptoms, however, decrease with age.<sup>5</sup>

## The atopic march

Atopy refers to the increased sensitivity of IgE to a specific antigen, which in turn, results in a hypersensitive response upon exposure toward the specific allergen in question.<sup>6</sup> 'Atopic march' is a term that refers to the development of various atopic diseases that may develop during childhood. The atopic march may also refer to how the sequence of clinical symptoms and atopic disease manifest during childhood growth and development.<sup>7</sup> The initial development of atopy has been linked to various predisposing risk factors. These include a genetic predisposition, decreased exposure to infections and endotoxins, postnatal antibiotic use, obesity, tobacco smoke, air pollutants, exposure to allergens, maternal weight gain or obesity, gestational use of antibiotics and maternal stress.<sup>8</sup>

## Pathophysiology of atopy

There is vast evidence that shows that T-lymphocytes play a major role in allergic diseases. The T-helper cell type 1 (T<sub>h</sub>1)/T-helper cell type 2 (T<sub>h</sub>2) paradigm has been extensively studied and seems to be the major pathological pathway in allergic diseases. The paradigm explains the relationship between the T<sub>h</sub>1 and T<sub>h</sub>2 subsets of the T-lymphocyte. T<sub>h</sub>1 and T<sub>h</sub>2 subsets tend to differentiate from CD4<sup>+</sup>-naïve T-lymphocytes. This means that whenever a raised response towards either the T<sub>h</sub>1 or the T<sub>h</sub>2 subset occurs, the other will be reduced.<sup>9</sup> When there is a reduction in T<sub>h</sub>1 production, there are observed decreased levels of interferon gamma (IFN-γ), interleukin (IL)-2 and tumour necrosis factor (TNF)-β. This in turn leads to elevated levels of T<sub>h</sub>2 effect, owing to a decrease in



**Figure 1: The imbalance between  $T_H1$  and  $T_H2$**   
 IgG – immunoglobulin G,  $T_H1$  – T-helper cell type 1,  $T_H2$  – T-helper cell type 2

IgG production, which inhibits  $T_H2$  formation.<sup>9,10</sup> There are various risk factors that can predispose a patient towards the development of atopy. Refer to Figure 2.

Figure 1 illustrates the imbalance in  $T_H1$  and  $T_H2$  that leads to atopic diseases.<sup>10</sup>

**The role of histamine in allergy**

Histamine is an endogenous substance synthesised from histidine. It has the ability to elicit autacoid effects within peripheral tissues

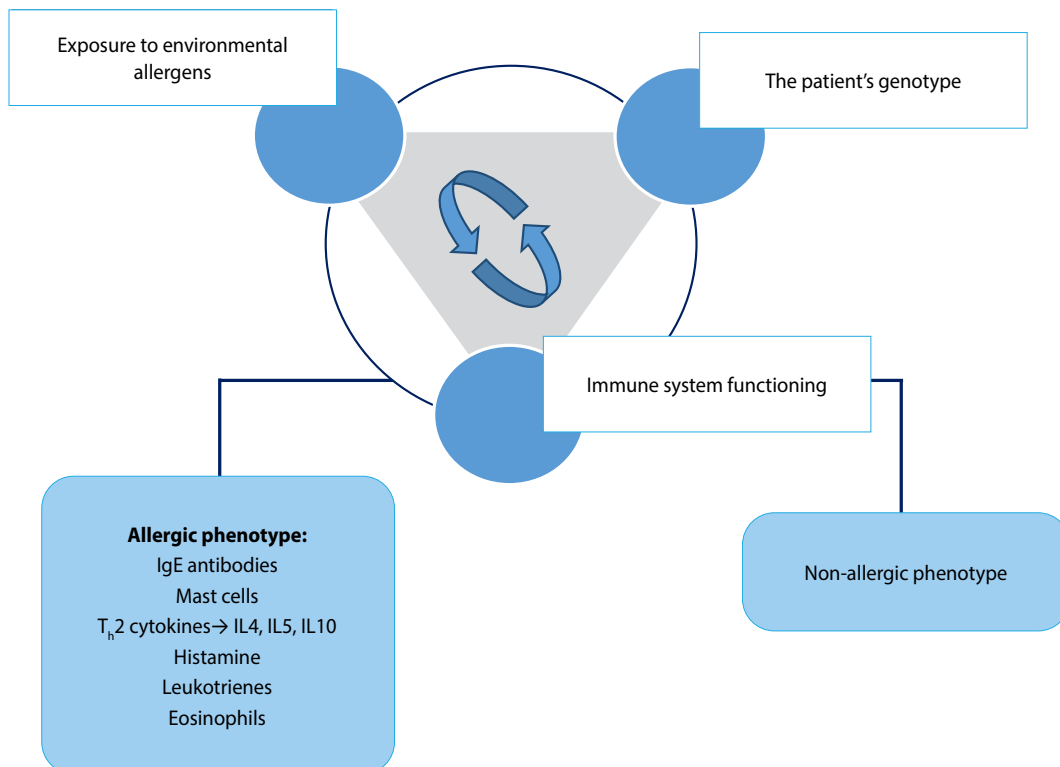
and also acts as a neurotransmitter within the central nervous system (CNS).<sup>11</sup> The role of histamine in the inflammatory process remains significant in understanding the pathophysiology thereof. The release of histamine in peripheral tissue areas is mediated by mast cell degranulation. This degranulation can be triggered in various ways. In allergic diseases, an interaction between IgE (immunoglobulin E) antibodies and suitable IgE antigens (i.e. the formation of antigen-antibody complexes) that causes allergic reactions (localised histamine release) or anaphylaxis (systemic histamine release), seems to be the major trigger.<sup>11</sup>

There are currently four identified histaminergic receptor subtypes (i.e. the  $H_1$ - to  $H_4$ -receptors). The  $H_1$ -receptor is the main active subtype in mediating acute allergic reactions. There are different effects that may be induced by  $H_1$ -receptor stimulation. Some of these effects lead to allergic conditions, which include allergic rhinitis and conjunctivitis, urticaria, pruritus and angioneurotic oedema.<sup>11</sup>

Stimulation of these receptors is also responsible for the vasodilatation and the increased vascular (capillary) permeability that accompanies allergic reactions and inflammation – erythema and oedema, including potentially fatal glottis oedema. Understanding histamine regulation assists in the type of treatment to be initiated in various allergic reactions. For instance, histamine is released systemically in anaphylaxis but the use of an antihistamine alone is not effective in treating anaphylaxis.

**Genetic predisposition**

Allergies tend to be familial, with patients who suffer from an allergy tending to have an increased risk of having children



**Figure 2: Risk factors for developing atopy<sup>2</sup>**

with some form of atopy.<sup>2</sup> There is vast evidence that shows that T-lymphocytes play a major role in allergic diseases. Several studies have looked at the role of genetics in allergic diseases. Some studies have had mitochondrial RNA (miRNA) as the main focus of such investigations. The earlier studies have shown that several types of miRNA augment the sensitivity of T-cells to peptide antigens. Evidence suggests that inhibition of miR-181a expression in immature T-cells significantly decreases sensitivity to antigens and enhances the impairment of T-cell selection. T-cell apoptosis is crucial in regulating both the length and strength of T-cell responses. MiR-21 has also been extensively studied, showing significant upregulation during T-cell activation and plays a role in the suppression of apoptosis in activated T-cells. It is therefore essential to understand the role of various miRNA in T-cell regulation as the development of polarised  $T_H$  cells is central to the pathogenesis of allergic inflammation because allergic inflammation is predominately a  $T_H2$  response.<sup>12</sup>

### Allergen exposure

Exposure to an allergen in individuals with an atopic disease increases the risk of developing a hypersensitivity reaction, regardless of the level of antigen exposure. The evidence showing that immune sensitisation is not dependent on the level of allergen exposure gives credibility towards a belief that the existence of atopic disease is hereditary. On the other hand, low levels of allergen exposure are not sufficient to produce a response, while high levels of allergen exposure induce tolerance toward that allergen, i.e. desensitising it.<sup>13</sup>

### Infections and endotoxin exposure

The hygiene hypothesis is applied in most atopic diseases. It predicts that the prevalence of atopic diseases is decreased when a child is exposed to more infectious agents. It is estimated that the exposure to animals, viruses, bacteria and various endotoxins makes children less likely to develop an atopic disease. The hygiene hypothesis emerges from the understanding that bacterial, viral and endotoxin factors trigger an immune response of  $T_H1$  lymphocytes.  $T_H1$  lymphocytes increase the production of IgG antibodies.  $T_H1$  (through IgG) indirectly suppresses the activity of  $T_H2$  which mediates the release of various cytokines including IgE. These  $T_H2$  cytokines are common culprits in the development of allergic diseases.<sup>2,7,14,15</sup>

### Intestinal flora

The presence of microbes in the walls of the intestinal tract helps to regulate an immune response. Exposure to microbial flora within the gastrointestinal tract early in life allows for a change in the  $T_H1:T_H2$  cytokine balance, favouring a  $T_H1$  cell response. A shift in the microbial balance initiates a change in immune response.<sup>2</sup> The evidence then suggests that exposure to high dosages of antibiotics in early neonates may alter the composition of intestinal flora, leaning towards an immune response with elevated levels of  $T_H2$ . The elevated  $T_H2$  leads to increased IgE production and therefore the likelihood of developing an atopic disease.<sup>16</sup>

## Common allergic diseases across the globe

Several allergic conditions are described in more detail below.

### Rhinitis

Rhinitis is an inflammation of the nasal mucosa. According to the Australasian Society of Clinical Immunology and Allergy (ASCI) there are various causes of rhinitis which include: allergies (hay fever), increased sensitivity to irritants such as smoke, temperature changes or the overuse of decongestant nasal sprays.<sup>17</sup> The most common antigens for allergic rhinitis are inhaled allergens, the most concerning being dust mites, animal dander and pollen.<sup>17,18</sup>

Allergic rhinitis (AR) affects approximately 20% of the world population and is considered to be the most common chronic disease.<sup>19</sup> AR is a type 1 allergic disease which reduces quality of life depending on the severity.<sup>20</sup> Exposure to nasal allergens stimulates an IgE-mediated type 1 hypersensitivity reaction, resulting in symptomatic reactions to the allergen. The early characteristic symptoms of allergic rhinitis are rhinorrhoea, nasal congestion and sneezing.<sup>19-21</sup> AR can also be associated with various conditions such as bronchial asthma, allergic conjunctivitis, rhinosinusitis and others.<sup>21</sup>

The inhalation of nasal antigens in sensitised individuals causes the antigens to pass through mucosal epithelial cells, binding to IgE antibodies on mast cells distributed over the nasal mucosa. The antigen-antibody complex stimulates an IgE-mast-cell-mediated early-phase response.<sup>19</sup> Chemical mediators, such as histamine and peptide leukotrienes (LTs), are released from mast cells. The release of these mediators causes irritation to the sensory nerve endings and mucosal blood vessels, leading to early phase reaction symptoms (i.e. sneezing, watery rhinorrhoea, and nasal mucosal swelling).<sup>20</sup> The early phase symptoms usually appear within 30 minutes after exposure to an allergen. Late-phase response results in tissue damage and remodelling, appearing 24 hours after allergen exposure.

The presence of an antigen in the nasal mucosa leads to the stimulation of cytokines, chemical mediators and chemokines which respond by releasing various inflammatory cells, such as activated eosinophils which infiltrate the nasal mucosa. Leukotrienes produced by these inflammatory cells cause nasal mucosal swelling.<sup>19,20</sup>

### Sinusitis

Sinusitis is defined as inflammation of the paranasal sinus mucosa. Sinusitis has been replaced with the more correct term 'rhinosinusitis'.<sup>22</sup> The term rhinosinusitis is given preference over sinusitis because sinusitis, in most instances, is almost always followed by inflammation of the adjacent nasal mucosa. The classification of rhinosinusitis is usually based on whether it is acute rhinosinusitis (ARS) or chronic rhinosinusitis (CRS). Many scientists concur on the duration of CRS being longer than 12 weeks while ARS still has different duration classifications from different scientists but usually less than 12 weeks.<sup>23</sup>

### Acute rhinosinusitis

ARS occurs as a result of inflammation of the nasal mucosa mainly due to bacterial, fungal, or viral infections, as well as allergies or exposure to inhaled irritants.<sup>24</sup> It is essential to properly diagnostically distinguish bacterial ARS from viral ARS, to assist with the treatment plan. Treatment in bacterial ARS involves antibiotics which would be inappropriate if used for viral ARS.<sup>23,24</sup>

### Chronic rhinosinusitis

CRS affects about 10–15% of the adult population in industrialised countries such as Europe and the US, and is one of the most reported chronic conditions.<sup>25</sup> It has been observed over the years that there are multiple variants of CRS which include characterisation of the disease by chronic infection, non-eosinophilic inflammation, chronic hyperplastic eosinophilic sinusitis (CHES), aspirin-exacerbated respiratory disease and allergic fungal sinusitis.<sup>26</sup> When there is chronic inflammation in the nasal mucosa, the observed result is mucosal swelling (including polyposis), increased mucus secretion, airway obstruction, and blocked sinus drainage. The inability of the nose to eliminate bacteria, viruses, fungi and allergens creates an environment of chronic inflammation which then results in a chronic nasal disease.<sup>24</sup> Some patients with chronic sinusitis present with massive submucosal eosinophilic infiltration. Eosinophilic sinusitis is characterised by multiple nasal polyps, viscous rhinorrhoea, and olfactory disorder, and is often complicated by asthma. Eosinophilic sinusitis is extremely intractable and resistant to surgery, resulting in repeated relapses. Oral corticosteroid therapy often results in a complete response.<sup>20</sup>

### Allergic rhinosinusitis

The presence of an allergen can cause inflammation of the sinus mucosa, which may be acute or even chronic. This inflammation prevents the usual clearance of bacteria from the sinus cavity, increasing the chances of developing secondary bacterial sinusitis. It is estimated that more than 50% of people with allergic rhinosinusitis have clinical or radiographic evidence of CRS. About 25–58% of people with rhinosinusitis have some form of inhaled allergen sensitisation. This is confirmed by the presence of raised IgE, which leads to an active immune response. Evidence supports the suggestion that CRS could be an atopic disease driven by IgE sensitisation to aeroallergens.<sup>26</sup> The symptoms of allergic rhinosinusitis include: rhinorrhoea, nasal congestion, facial pain, fever, cough, sore throat and fatigue.<sup>27</sup> These symptoms significantly reduce the quality of life of individuals, creating inconvenience for both people and the economy.

### Atopic dermatitis

Atopic dermatitis (AD) is one of the most common chronic inflammatory disorders of the skin with a strong link to genetic predisposing factors. It affects approximately 20% of children and 1–3% of adults in industrial countries.<sup>28</sup> There is a clearly identified hyper-proliferative cutaneous disorder in AD that is associated with a defective skin barrier and a mixed  $T_H1/T_H2$  inflammatory response. This exposes the skin and makes it susceptible to cutaneous infections and moderate to severe pruritus.<sup>12</sup> A major number of patients suffering from AD have been observed to have elevated serum levels of total IgE and allergen-specific IgE, with approximately 50% of individuals testing positive on

**Table 1:** Potential causes of conjunctivitis<sup>30,31</sup>

Conjunctivitis				
Infectious	Causative agent	Type of discharge	Ocular symptoms	Accompanying symptoms
Viral	Adenoviruses (most common cause)	• Watery	• Red eye	Pharyngoconjunctival fever • High fever • Pharyngitis • Enlargement of the periauricular lymph nodes • Bilateral conjunctivitis Keratoconjunctivitis (severe) • Oedema of the sclera • Hyperaemia
Bacterial	<i>H. influenzae</i> * <i>S. pneumoniae</i> * <i>S. epidermidis</i> <i>S. viridans</i> <i>S. aureus</i> <i>Moraxella catarrhalis</i> * <i>Neisseria gonorrhoeae</i>	• Mucopurulent/purulent	• Red eye • Oedema of the sclera • Pain in the eye	• Swelling of the eyelid • Mattering and sticking together of the eyelids in the morning
Non-infectious				
Allergic	Allergens (pollen, animal dander)	• Watery	• Red eye • Itching • Burning sensation • Conjunctival oedema	• Swelling of the eyelid • Runny nose • Blurry vision

an atopy patch test.<sup>28</sup> There are several allergens that lead to the exacerbation of AD which may include airborne pathogens, e.g. pollen, and various foods. Avoidance of identified allergens usually has significant benefit to patients with AD.<sup>6,28</sup>

### Eosinophilic oesophagitis

Eosinophilic oesophagitis is an allergic condition that has recently emerged and has been reported in all continents except Africa.<sup>12</sup> Observed inflammation of the oesophagus with abnormal eosinophils in allergic reaction are the main characteristics of the disease. Potential allergens include cross-reacting molecules, which are common between pollen antigens or latex food allergens. The emergence and prevalence of this disease is becoming a global concern and requires more investigation.<sup>1,12,20</sup>

### Allergic conjunctivitis

Allergic conjunctivitis is an inflammatory response of the conjunctivae to allergens such as pollens, environmental antigens (e.g. dust), and animal dander.<sup>29</sup> Hyperaemic conjunctivitis is a common type of conjunctivitis; most patients show symptoms of ocular itching, lacrimation, hyperaemia, eye discharge, etc. Severe symptoms cause eyelid swelling. A number of conditions may present with conjunctivitis (red eye), but it would be best to try and differentiate allergic conjunctivitis from other eye conditions. Knowledge of eye conditions, how they present and their prevalence is important. Before a likely diagnosis is made the following should be considered: the causative agent involved, types of discharge, ocular symptoms and lastly, other accompanying symptoms (Table I).<sup>30</sup>

#### Types of allergic conjunctivitis

Allergic conjunctivitis can be differentiated into three types: acute allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC). The differences between these three types are listed in Table II.<sup>5</sup>

#### The role of the pharmacist in the management of allergic conjunctivitis

Pharmacists are exposed to a lot of patients that report acute allergic conjunctivitis and they are the first healthcare professionals

that patients approach. Pharmacists should be able to assess patients individually and follow a stepwise approach. They also play an important role in facilitating the selection of artificial tear solutions, ensuring that the solutions are preservative free, suggesting topical antihistamine-decongestant products and oral antihistamines. The pharmacist also provides information or counsels patients on palliative care, such as avoiding allergens and the appropriate storage of medicine, i.e. the refrigeration of topical solutions.<sup>32</sup> Ultimately, referral may be necessary when patients present with comorbidities, symptoms that overlap with other conditions, no response to over-the-counter treatment, contact lens users, severe signs and symptoms.<sup>33,34</sup>

#### Emerging therapies for allergic conjunctivitis

Topical combination of antihistamine/mast cell stabilisers, i.e. olopatadine, provides an additional, immediate relief benefit as well as the long-term relief from the mast cell stabilisation. This combination also has the additional advantage of once-daily dosing. There is a recognised need for medications that demonstrate rapid onset and a prolonged duration of action. The 24-hour dosing provides maintenance during symptomatic periods without any exposure to preservatives because of fewer instillations. It also promotes compliance. A higher concentration of olopatadine (antihistamine/mast cell stabiliser) is the newest combination therapy.<sup>35</sup> Olopatadine, when compared to sodium cromoglycate, showed that the more expensive olopatadine had fewer patient return visits.<sup>5</sup> Bepotastine, prescription-only drops administered twice daily, has a very high specificity for the H<sub>1</sub>-receptor, meaning that it is specific for the ocular itch experienced in allergic conjunctivitis. It also has additive effects on nasal congestion, rhinorrhoea, nasal itching and ear or palate itching.<sup>36</sup>

### Asthma

Asthma is one of the most common chronic inflammatory diseases that affect both children and adults. The inflammatory process causes hyper-responsiveness in the bronchial tree, with reversible airflow obstruction. Inflammation of the bronchial tree may result in airway constriction via smooth muscle contraction, the hyper-secretion of mucus, bronchial hyper-responsiveness,

**Table II:** Differences between the three types of allergic conjunctivitis<sup>5</sup>

Type of allergic conjunctivitis	Onset	Causes	Allergens
Acute allergic conjunctivitis	Sudden onset, develops rapidly (within 30 mins) and resolves immediately in the absence of the allergen (within 24 hours)	Environmental exposure	
SAC	Progressive onset and occurs gradually over days to weeks	Specific allergen	<ul style="list-style-type: none"> <li>• Tree pollen in spring</li> <li>• Grass pollen in summer</li> <li>• Wood pollen in late summer or autumn</li> </ul>
PAC	It is mild and chronic and can either increase or decrease in severity	Year-round environmental exposure	<ul style="list-style-type: none"> <li>• Dust mites</li> <li>• Animal dander</li> <li>• Moulds</li> </ul>

and additional narrowing of the airway due to mucosal oedema and sloughing of the epithelial cells.<sup>12</sup>

Allergic asthma is observed to be the most common type of asthma, caused mainly by inhaled allergens, inducing an immune system response.<sup>12</sup> The implementation of therapy must be done after accurate classification of asthma severity. This assists in reviewing the management of the condition when periodic assessment for asthma control has been established. Diagnosing asthma is based on two tools viz. identification of a characteristic pattern of respiratory symptoms and expiratory airflow limitation; these differ for each patient.<sup>37</sup>

### Management of allergic conjunctivitis

Allergic diseases can be strategically managed both non-pharmacologically and pharmacologically.<sup>38</sup> The use of pharmacological preparations is usually preferred for use when non-pharmacological methods prove ineffective or insufficient in alleviating the allergic symptoms. Different pharmaceutical preparations (systemic, intranasal, topical, etc.) are used depending on the symptoms and type of allergic disease.<sup>29,38</sup>

Topical therapy is either made up of combination drugs such as an antihistamine and a vasoconstrictor, or antihistamine with mast cell stabilising properties. The former are found over-the-counter, the vasoconstrictor targeting the ocular redness and the antihistamine targeting the allergic symptoms. An example is the tetryzoline/antazoline combination; however, it may cause increased redness for several days after use.<sup>5</sup> The latter have a dual mechanism of action; they block histamine receptors and they also stabilise mast cells and inhibit their degranulation which in turn limits the release of histamine, tryptase and prostaglandin D<sub>2</sub>. They also have an effect on leukocyte activity. These drugs are dosed twice daily and as prophylaxis they require two weeks of therapy to reach their maximum effect. Antihistamines with

mast cell stabilising properties can cause burning, stinging and irritation, headaches or ocular dryness when instilling the eye drops and these adverse effects can be avoided by refrigerating the drops.<sup>5</sup>

### Local vs systemic antihistamines in the treatment of allergic conjunctivitis

The results of randomised trials indicate that topical medications are more effective when compared to oral therapies when used for ocular conditions.<sup>5</sup> The systemic use of antihistamine only partially relieves ocular allergic symptoms<sup>32</sup> and patients may also experience systemic adverse effects such as drowsiness and dry mouth.<sup>34</sup> Therefore, topical administration especially of a combination (antihistamine/decongestant) is more effective for ocular allergic symptoms. However, in the situation where oral therapy is used, the second-generation antihistamines are preferred as they cause less sedation because of their reduced ability to cross the blood–brain barrier.<sup>32,33</sup>

### Local decongestants

Local decongestants are mainly sympathomimetic drugs that stimulate  $\alpha_1$ -adrenergic receptors producing vasoconstriction. This in turn decreases mucosal oedema and local vasodilation.<sup>38</sup> Examples of the most commonly used drugs include xylometazoline, phenylephrine and oxymetazoline.<sup>39</sup> Local decongestants are usually indicated to reduce acute symptoms as prolonged use can produce undesirable effects to the user.<sup>38</sup> After persistent use (usually more than five days), rebound rhinitis and conjunctivitis medicamentosa start to appear. Oxymetazoline and xylometazoline have a long-acting effect on the  $\alpha_1$ -receptor, whereas phenylephrine has a shorter duration of action, lasting up to approximately four hours.<sup>40</sup> The mechanisms of action of the local decongestants illustrated in Figure 3 involve targeting the vasodilatation of the mucosal oedema (i) that causes nasal

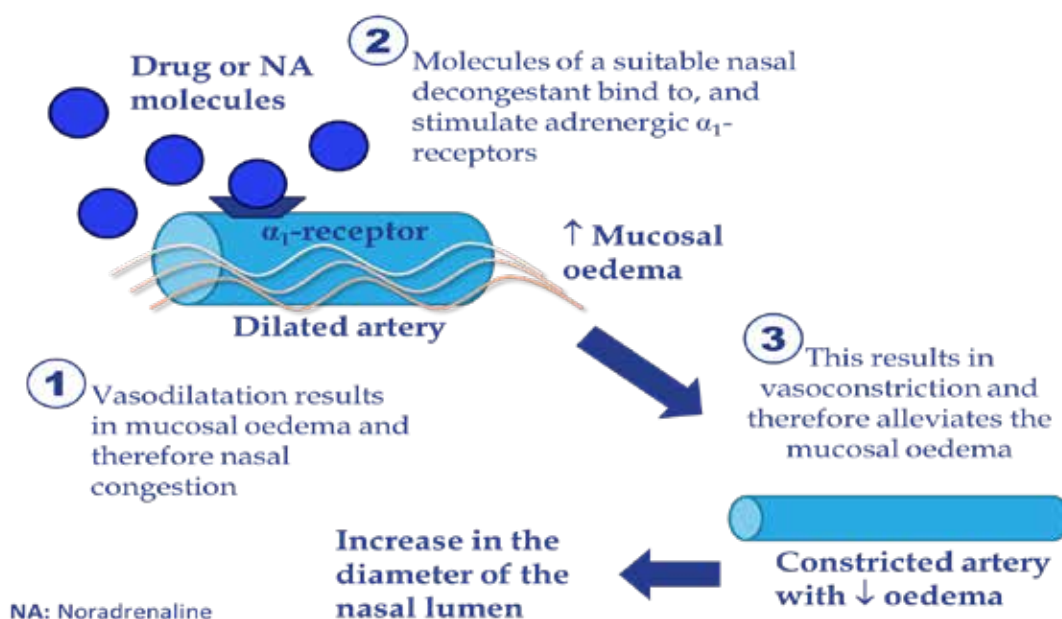


Figure 3: The mechanisms of action of local decongestants

congestion; (ii) the molecules of a suitable nasal decongestant bind to, and stimulate adrenergic alpha 1-receptors; (iii) resulting in vasoconstriction, therefore alleviating the mucosal oedema, and increasing the diameter of the nasal lumen.

### Systemic decongestants

These agents stimulate  $\alpha_1$ -receptors producing vasoconstriction, reducing oedema, redness and itching. Their preparations usually contain an antihistamine. It is important to note that combination therapy of a systemic decongestant and an older-type  $H_1$ -antihistamine can produce drowsiness and a lack of motor coordination. Systemic decongestants available in South Africa include pseudoephedrine, phenylpropanolamine and phenylephrine. The use of phenylpropanolamine has produced sub-arachnoid bleeding with haemorrhagic stroke in women

using it as an appetite suppressant. The total daily dosage of phenylpropanolamine should not exceed a 100 mg.<sup>38</sup>

### Corticosteroids

Glucocorticosteroids can be used for various allergic conditions such as asthma, allergic rhinitis and with minimal use in allergic conjunctivitis. They exert their pharmacological action by modifying protein synthesis through regulating transcription, and indirectly by modifying the activity or half-life of transcription factors and mRNA. The currently available intranasal corticosteroids include: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. The newer agents, namely mometasone, fluticasone, and ciclesonide, are also administered intranasally and result in minimal systemic effects.<sup>39</sup> The most common local side-effects experienced with the intranasal cor-

**Table III:** The differences between first- and second-generation antihistamines<sup>43</sup>

	Older, first-generation $H_1$ -antihistamines	Newer, second-generation $H_1$ -antihistamines
<b>Drug examples</b>	Promethazine Chlorpheniramine Dexchlorpheniramine Hydroxyzine Cyclizine	Cetirizine and levocetirizine Loratadine Ebastine Fexofenadine Mizolastine Rupatadine
<b>Frequency</b>	Usually administered in 3–4 daily dosages.	Usually administered once or twice a day.
<b>Mechanism of action</b>	Potent blockers of $H_1$ , $\alpha_1$ and muscarinic receptors.	Selective $H_1$ -receptor antagonists.
<b>Blood–brain barrier</b>	Cross the blood–brain barrier (lipophilicity, low molecular weight and lack of recognition by the p-glycoprotein efflux pump).	Generally, do not cross the blood–brain barrier at recommended dosages (lipophobicity, high molecular weight and recognition by the p-glycoprotein efflux pump).
<b>Indications</b>	Chlorpheniramine displays lower levels of sedation than many of the other examples in this group, and may therefore be better suited to the management of allergic reactions.	Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria for adults and children aged 12 years and older.
	The options for sedation include hydroxyzine, promethazine and diphenhydramine. However, more suitable agents may be used in the management of insomnia.	Fexofenadine has the shortest half-life of the systemic agents. Furthermore, it also does not display any $H_1$ -receptor occupancy inside the central nervous system at therapeutic dosages.
	As an antiemetic agent, choose from cyclizine ( <i>syn.</i> meclizine), diphenhydramine, hydroxyzine or promethazine, for example. First-generation $H_1$ -antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo.	Cetirizine has the greatest likelihood of displaying some degree of $H_1$ -receptor occupancy inside the central nervous system, which may result in some level of sedation, albeit at higher-than-recommended dosages.
<b>Side-effects</b>	Potentially cause side-effects, such as: Sedation Drowsiness and dizziness Hyperactivity (meta-reaction) Insomnia Convulsions Impaired driving performance Fatigue and lassitude (well documented)	Do not cause relevant side-effects (sedation, fatigue, hyperactivity and convulsions) in the absence of drug interactions.
	Anticholinergic side-effects, including a dry mouth, urinary retention, gastrointestinal upset and appetite stimulation.	Minor side-effects include: Nausea Light headedness Drowsiness Headaches Agitation and a dry mouth
<b>Toxicity</b>	Case reports of toxicity are regularly published.	There have been no reports of serious toxicity.
<b>Overdose</b>	A lethal dosage has been identified in infants and young children.	Do not cause fatality in overdose.

ticosteroids include dryness, stinging, burning, and epistaxis. Chronic use of topical corticosteroids may lead to atrophy of the nasal mucosa. It is therefore advisable to use these agents for the shortest time possible to prevent unpleasant adverse effects associated with long-term use.<sup>41</sup> Systemic corticosteroids such as hydrocortisone and prednisone can be used in chronic dermatitis to reduce the frequency of allergic flares.<sup>28</sup>

### The H<sub>1</sub>-antihistamines

H<sub>1</sub>-antihistamines based on pharmacological classification are grouped into different generations. This system of classification is based on their target receptors as well as side-effect profile.<sup>42</sup> The H<sub>1</sub>-antihistamines are classified into first-generation (older, sedating, multi-potent blockers) and second-generation (non-sedating, newer) antihistamines. First-generation antihistamines include promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine whilst the second-generation antihistamines include cetirizine (and levocetirizine), loratadine, ebastine, fexofenadine and mizolastine. The most significant difference (refer to Table III) between the two classes is that first-generation H<sub>1</sub>-antihistamines have the ability to cross the blood–brain barrier and the second-generation non-sedating H<sub>1</sub>-antihistamines have very limited ability, if none at all, to cross the blood–brain barrier. It is also important to note that two generations of systemic (oral and/or parenteral) agents, topical (including intranasal and ophthalmic) H<sub>1</sub>-antihistamines are available as well.<sup>11,18,40</sup>

#### First-generation H<sub>1</sub>-antihistamines

These older H<sub>1</sub>-receptor blockers have been shown to have sedative and multi-potent receptor-blocking abilities. Their ability to cross the blood–brain barrier distinguishes them from the newer generation H<sub>1</sub>-antihistamines. The chemical structure of the first-generation antihistamines permits them to have a certain degree of non-selectivity, exerting antagonistic effects of an antimuscarinic or anticholinergic, antihistaminergic, α<sub>1</sub>-adrenergic blocking, anti-serotonergic and local anaesthetic nature. Because of their wide range of receptor blocking, the first-generation H<sub>1</sub>-antihistamines have a variety of indications and uses, which range from allergies and rhinoconjunctivitis, to nausea and vomiting, motion sickness and insomnia. Their effects on multiple receptors,

on the other hand, also have undesirable effects (refer to Table IV) and are not recommended for use in patients who suffer from glaucoma, benign prostatic hyperplasia and in cardiac patients (i.e. ischaemic heart disease, myocardial infarction and congestive heart failure).<sup>43</sup>

The following drugs in this group are of note:

- The options include hydroxyzine, promethazine and diphenhydramine. These drugs are used in the management of insomnia but there are more suitable agents that may be used.
- Cyclizine (*syn.* meclizine), diphenhydramine, hydroxyzine or promethazine, are examples of antiemetic agents. First-generation H<sub>1</sub>-antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo.
- Chlorpheniramine is better suited for use in allergic reactions due to its relatively lower sedation levels than the other first-generation antihistamines.

It should be noted that these “older” drugs have never been optimally investigated and profiled from a clinical pharmacology perspective.

#### Second-generation H<sub>1</sub>-antihistamines

Second-generation H<sub>1</sub>-antihistamines are relatively newer antihistamines that do not possess the ability to cross the blood–brain barrier. They also have no antiemetic, anticholinergic and central nervous system effects unlike the first-generation antihistamines. Drugs like fexofenadine are actively transported into the lumen of the gut, kidney and brain by p-glycoproteins, which restrict their ability to accumulate and cause unwanted side-effects. However, agents such as rifampicin, which induce p-glycoprotein, may increase the clearance of fexofenadine and reduce its efficacy.<sup>45</sup> Second-generation H<sub>1</sub>-antihistamines are mostly used as a once-daily dose with minimal risk of developing tolerance. The long-term safety of the second-generation H<sub>1</sub>-antihistamines, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, has been documented in randomised controlled trials lasting 6–18 months in adults and in children as young as 1–2 years’ old.<sup>46</sup>

Rupatadine fumarate is a newly-launched, second-generation, long-acting histamine antagonist (H<sub>1</sub>-receptor antagonist) and platelet-activating factor-receptor inhibitor. Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria in adults and children aged 12 years and older. It inhibits the degranulation of mast cells and the subsequent release of cytokines, more specifically of tissue necrotising factor which is available in mast cells and monocytes.<sup>48</sup>

Ophthalmic (eyedrop) preparations include levocabastine, epinastine, olopatadine and ketotifen (the latter also acts as a mast cell stabiliser). Levocabastine, in addition to azelastine, is also available as a nasal spray for use in patients who suffer from allergic rhinitis.<sup>47</sup>

**Table IV:** The adverse effects of first-generation antihistamines, as reflected by receptor activity<sup>44</sup>

Receptor antagonistic interaction	Side-effects
Histamine <sub>1</sub> receptor	A reduction in central nervous system neurotransmission, sedation, reduced cognitive and neuro-psychomotor performance, and an increased appetite.
Muscarinic receptor	Xerostomia, urinary retention and sinusoidal tachycardia.
α-adrenergic receptor	QTc-interval prolongation and ventricular arrhythmias.
Serotonergic receptor	An increased appetite.
IKr and other cardiac channels receptors	QTc-interval prolongation and ventricular arrhythmias.



### The leukotriene-receptor antagonists

Examples of leukotriene receptor antagonists include zafirlukast and montelukast. They are competitive antagonists of the cysteinyl leukotriene receptor-1 (cysLT-1). They have the advantage of oral administration. Montelukast is also available as a sprinkle and in a chewable tablet form for convenient use in paediatrics. Montelukast presents an additional option in the management of seasonal allergic rhinitis in children with asthma.<sup>50</sup>

### Mast cell stabilisers

They act by stabilising mast cells, thus preventing the release of histamine. The maximum effect is reached after 5–14 days administration, and they are dosed more frequently than topical antihistamines, i.e. four times daily. Therefore, they are not used in the treatment of acute allergic conjunctivitis, and they are reserved for the treatment of SAC in patients that cannot tolerate other therapy.<sup>5</sup>

### Conclusion

Allergic conjunctivitis seems to be on a constant rise affecting a large percentage of the population. Allergic conjunctivitis can decrease quality of life and productivity, and the condition can be exacerbated by the presence of comorbid conditions such as rhinitis. The current therapies for the treatment of allergic conjunctivitis, such as antihistamines, mast cell inhibitors and anti-inflammatory drugs are still considered to be effective. The role of the pharmacist is to follow a stepwise approach to treatment. The topical antihistamine/mast cell stabiliser formulations are the first treatment approach because of their ability to relieve symptoms rapidly and they are suitable and well-tolerated for long-term use. However, the development of newer drugs with prolonged duration of action and specificity provides more options. The newly available olopatadine has demonstrated superior effectiveness and is a potential agent of choice in the treatment of SAC or PAC.

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