Antihistamines and allergies

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Abstract

Allergy is a very common chronic health condition with a rising incidence. Allergic reactions are immune-mediated and associated with considerable morbidity that impact on the quality of life and pose a socio-economic burden. It is important to identify triggers and to understand the role of the complex immune system. Antihistamines are the most commonly prescribed medicine to treat allergies. Although the efficacy of H_1-receptor antagonists is very similar, their pharmacological properties differ. As a custodian of medicine, the pharmacist should have a good understanding of an allergic reaction, how to treat it appropriately and how to individualise therapy. This review focuses primarily on common IgE-mediated allergic conditions treated with antihistamines.

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Introduction

Allergy is defined as a damaging immune response by the body to a substance to which it has become hypersensitive. It is part of an immune system response known as hypersensitivity reactions.[1] The prevalence of allergy has risen significantly in the past few decades and is reported to be in the range of 30–40% globally. Children are more prone to have allergies compared with adults.[2] A comprehensive survey conducted worldwide (ISAAC Phase III) concluded that every third child below the age of 18 years, is allergic to one or other allergen.[3] The symptoms of asthma, allergic rhinitis and atopic eczema have been increasing over the years in the adolescent population of Africa.[4]

In South Africa the exposure to allergens varies between the rural and urban areas.[5] The hygiene hypothesis is a concept related to lifestyle changes and possibly explains the increasing incidence of both autoimmune and allergic diseases in western countries and more recently in developing countries.[5,6] Infants and children in developing countries are more exposed to infections due to problems related to sanitation, clean drinking water, malnutrition and overcrowding.[2]

The term 'atopy' is derived from the Greek word *atopos*, meaning 'out of place' and is used synonymously with allergy in describing immunoglobulin E-mediated diseases. Atopic individuals are genetically predisposed to develop one or more allergic disorder, including certain food allergies. It has a strong familial[2] incidence – if both parents are atopic, the child has a 50% chance of suffering from an allergic disorder.[7] These individuals however may or may not present with symptoms of allergy. The most common immune-mediated conditions, namely atopic dermatitis (eczema), allergic rhinitis (hay fever) and asthma, are referred to as the atopic triad. Atopic dermatitis most often presents as the first allergy in this triad, suggesting the start for subsequent allergic diseases. This sequence of progression is referred to as "the atopic march", with some clinical signs becoming more prominent while others subside.[8]

Allergies can decrease the quality of life, lead to absenteeism from school or the workplace, cause significant morbidity and even mortality, and furthermore pose a huge health burden.[1,6] It is therefore important to understand this disorder and treat it appropriately. Good allergy treatment is based on a patient's medical history, results of allergy tests and severity of symptoms. Three treatment options are advocated: allergen avoidance, medicine options and/or immunotherapy.[7]

The immune system and sensitisation

A complex but vital network of cells and lymphoid organs make up the immune system.[9] It is a highly interactive network, which responds on the basis of all body tissues, infections, normal flora bacteria, and various environmental agents.[10] Anything that can trigger this immune response is known as an antigen. When the immune system responds to a seemingly harmless foreign substance, the antigen is referred to as an allergen.[11]

Acquired (adaptive) immunity requires prior exposure to an antigen and thus takes time to develop after the initial encounter with a new invader.[12]

The immune response in allergy begins with sensitisation.[13] All immune cells originate as immature stem cells in the bone marrow. They respond to cell signalling molecules (cytokines e.g.

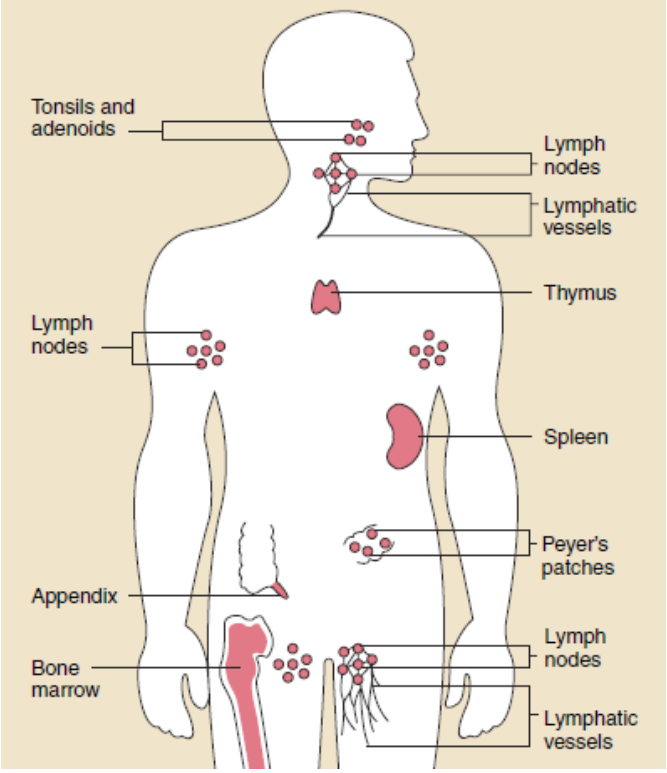


Figure 1: Lymphoid organs[11]

interleukins) and differentiate into specific immune cell types, e.g. T cells, B cells (the two main types of lymphocytes) or phagocytes.

To understand the immunobiological mechanism of sensitisation, the interaction between allergens and relevant structural and immune cells during mucosal exposure and entry, are of utmost importance. These cells include the epithelial cells (cells of the first physical barrier), antigen-presenting cells (e.g. dendritic cells, macrophages), and T-helper cells and B cells. Each B cell is programmed to make one specific antibody and when triggered by antigen, gives rise to many large cells known as plasma cells.[11] T-helper cells (Th or $CD4^+$ cells) are divided into three broad classes: effector T-cells, memory T-cells, and T-regulatory cells. Effector T cells are further divided into TH_1, TH_2 and TH_{17}, based on the cytokines they produce.[14] With regards to allergic reactions, TH_2 cells are important as they produce interleukin IL-4 and IL-13. Interleukins are naturally occurring proteins that mediate communication between cells.[15] An example hereof is interferon-[gamma], a TH_1 cytokine that acts in conjunction with TH_2 (via the interleukins) in maintaining chronic allergic inflammation.[16]

Interleukin-4 and IL-13 act on B cells to promote the production of antigen-specific IgE. T-helper cells thus coordinate the immune response by communicating with nearby B cells to produce antibodies. Millions of identical antibodies are manufactured in the plasma cells and poured into the systemic circulation.[11] Different allergens stimulate the production of corresponding allergen-specific IgE antibodies. Once formed and released into the circulation, IgE binds to high affinity receptors on mast cells via its Fc portion.[13] The allergen specific receptor site is now available for future interaction with the allergen.

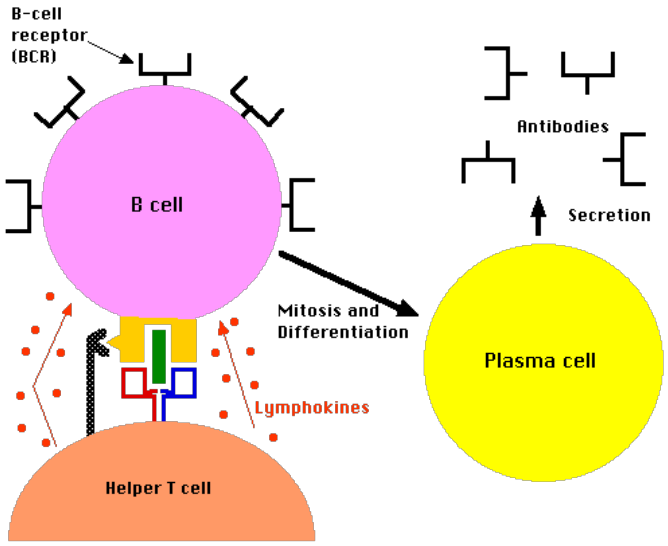


Figure 2: Specific immune cells[17]

After a person has been sensitised to an allergen, activation of mast cells occurs upon re-exposure to the particular allergen. Binding of allergen to IgE orchestrates the immune system to initiate a more intense and rapid memory response. A process of intra-cellular signalling is initiated after cross-linking of a sufficient number of mast cell/basophil IgE antibodies by allergen.[13] This leads to degranulation of cells and a subsequent release of a variety of preformed inflammatory mediators e.g. histamine, tumor necrosis factor-alpha (TNF-α), platelet-activating factor (PAF) and leukotrienes.[1] The cytokines released by basophils are important in the later phase of an allergic response.[2]

The role of mast cells in allergic reactions

Mast cells are highly specialised cells arising in the bone marrow and found in skin and in all mucosal tissues.[18] The major growth factor for mast cells is stem-cell factor (SCF) which binds to the receptor c-kit.[1] Mast cells are the only terminally differentiated

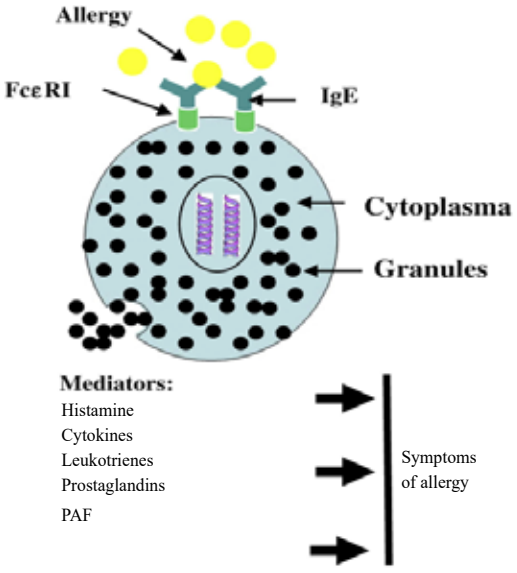
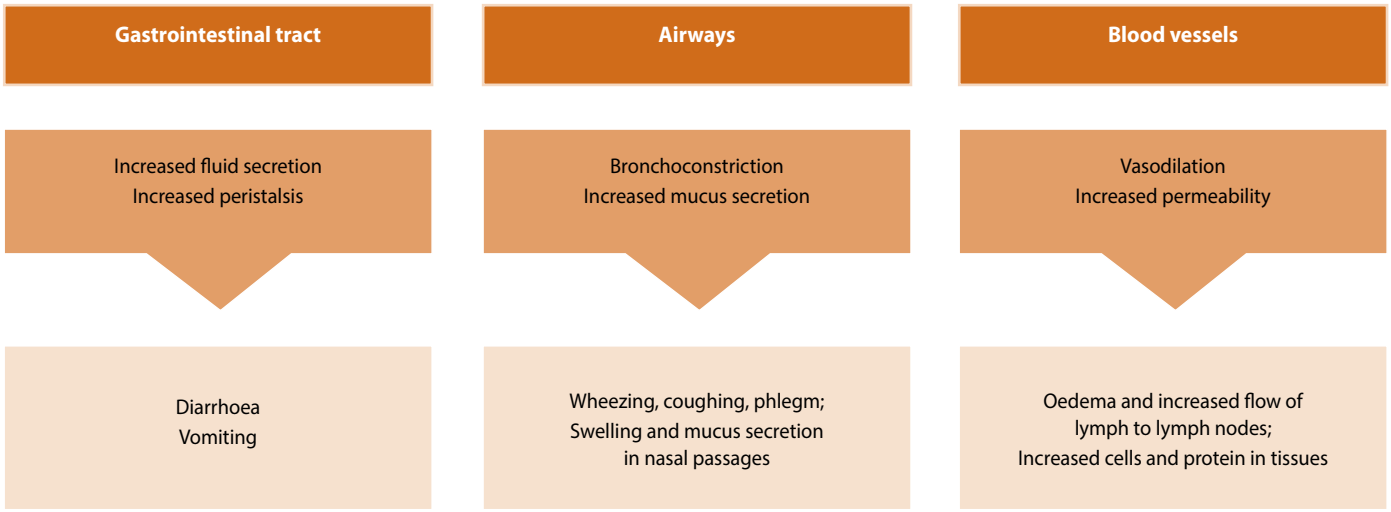


Figure 3: Activated mast cells[18]

Figure 4: Different effects on various tissues after mast cell activation[1]



haematopoietic cell that expresses the c-Kit receptor.[18] Mast cells express high-affinity receptors (FcεRI) on their surface and attempt to sustain a fixed number of these receptors unoccupied.[18] Mast cells regulate the IgE receptor expression. Immunoglobulin E antibodies bind to these receptor sites, waiting for their specific allergen to be encountered, resulting in activation of mast cells.[13]

Early and late phase allergic reactions

The early phase reaction (immediate hypersensitivity) occurs within minutes of exposure to the allergen. The late phase reaction occurs four to six hours after the symptoms of the early phase have subsided and can last for days or weeks.[13] The immediate allergic reaction is thus followed by a more sustained inflammation. The latter involves the recruitment of other effector cells e.g. TH_2 lymphocytes, eosinophils, and basophils which contribute significantly to the immunopathology of an allergic response.[1]

Types of allergic reactions

The Gell and Coombs classification system for hypersensitivity reactions is well known. There are four types of hypersensitivity reactions mediated by immunological mechanisms that cause tissue damage.[1] Of the four hypersensitivity reactions, Type I has the most clear-cut immunopathological correlation.

Allergic reactions are mediated by IgE and manifest clinically as anaphylaxis, allergic asthma, urticaria, angioedema, allergic rhinitis (hay fever), reactions to certain medicines, and atopic dermatitis.[14] A Type I allergy is evident within five to fifteen minutes after allergen exposure and therefore referred to as an immediate hypersensitivity.[20] Symptoms experienced by the patient vary and depend on the route of entry as well as the dose of the allergen.[1]

Preformed chemical mediators

Many different mediators are implicated in allergic reactions[2] and those released upon mast cell activation can be divided into three overlapping categories: preformed mediators, newly-synthesised lipid mediators, and cytokines and chemokines. Histamine, neutral proteases (e.g. tryptase), proteoglycans (e.g. heparin), and some cytokines (e.g. TNF-α) are preformed and contained in mast cell secretory vesicles (or granules).[14] These mediators are rapidly released into the extracellular environment and are responsible for many of the acute signs and symptoms of allergic reactions.[21]

Table I: Classification of allergy[19]

Coombs classification	Type I	Type II	Type III	Type IV
Type of reaction	Immediate hypersensitivity	Cytotoxic reaction	Immune complex reaction	Cellular immunity (delayed hypersensitivity, cell mediated
Associated antibodies	IgE	IgG, IgM	IgG, IgM	
Associated immune cells	Histiocytes, basophils, mast cells	Cytotoxic T cells, macrophages	Multinuclear leukocytes, macrophages	Sensitised T cells, macrophages
Target tissues/cells	Skin, respiratory system, intestines	Skin, erythrocytes, leukocytes, platelets	Skin, vessel, joint, kidney, lung	Skin, lung, thyroid gland, central nervous system etc.
Disorders	Urticaria, drug eruption*, asthma, allergic rhinoconjuctivitis, anaphylaxis	Haemolytic anaemia, bullous pemphigoid, idiopathic thrombocytopaenia	Cutaneous small-vessel vasculitis, serum sickness, glomerulonephritis	Contact dermatitis

*Drug eruption is an adverse drug reaction of the skin.

Table II: IgE-mediated allergic reactions[2]

Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Medicine Serum Venoms Peanuts	Intravenous (either directly or following oral absorption into the systemic circulation)	Increased vascular permeability Oedema Tracheal constriction Circulatory collapse Death
Acute urticaria	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis	Pollens House dust-mite	Inhalation	Oedema and irritation of nasal mucosa
Asthma	Animal dander Pollens House dust-mite	Inhalation	Bronchial constriction Increased mucous production Airway inflammation
Food allergy	Tree nuts Peanuts Shellfish Milk Eggs Fish	Oral	Vomiting Diarrhoea Pruritus Urticaria Anaphylaxis (rarely)

Histamine is derived by decarboxylation of the amino acid L-histidine. Except for storage in mast cell secretory vesicles, histamine is found in non-mast cell tissues, including the brain, where it functions as a neurotransmitter. Another site of histamine storage and release is the enterochromaffin-like cells of the fundus of the stomach where it stimulates the acid-producing parietal cells of the mucosa.[22]

Effects of histamine

The effects of histamine are mediated through H_1, H_2, H_3, and H_4 receptors located on target cells:

- H_1-mediated actions cause bronchial constriction and intestinal smooth muscle contraction (e.g. diarrhoea), increased nasal mucus production, and T cell neutrophil and eosinophil chemotaxis. Histamine is a powerful stimulant of sensory nerve endings, especially those mediating pain and itching. Oedema, induced by histamine, is associated with the separation of the endothelial cells (increased vascular permeability), which permits the transudation of fluid into the perivascular tissue. This effect is responsible for urticaria, signalling the release of histamine in the skin.[22]
- The effects mediated through the H_2 receptor increase vascular permeability, increase gastric acid secretion, and airway mucus production, but cause inhibition of neutrophil and eosinophil influx.
- An H_3 receptor is located in the brain, as well as on sympathetic nerve fibres innervating blood vessels in the nasal mucosa and heart.
- An H_4 receptor modulates TH_2 responses. In humans, the actions of histamine at the H_4 receptor provide a potent chemotactic pathway for human eosinophils.[21]

Antihistamines as pharmacological management

The goal of therapy is to relieve symptoms and prevent a severe reaction. Antihistamines are of value in the treatment of conditions such as allergic rhinitis, allergic conjunctivitis and chronic urticaria.[23] These agents block the actions of histamine by reversible competitive binding to H_1 receptors and thereby reducing histamine-mediated responses.[22] Antihistamines do not form the mainstay of treatment in cases of severe angioedema or anaphylaxis but are rather used as adjunctive therapy to adrenaline and other emergency medicines.[24] In the treatment of atopic dermatitis (eczema), antihistamines e.g. diphenhydramine, are used primarily for the sedative effect to reduce awareness of itching.[22]

H_1 receptor	• Sedation • Cognitive reduction • Appetite increase
Muscarinic receptor	• Xerostomia (dry mouth) • Urinary retention • Tachycardia
α-adrenergic receptor	• Hypotension • Dizziness • Reflex tachycardia
Serotonergic receptor	• Appetite increase
Cardiac channels	• QT prolongation • Ventricular arrhythmia

Figure 5: Adverse effects of first-generation H_1-receptor antagonists[25]

Table III: Chemical classification of H_1-receptor antagonists

Alkylamines	Ethanolamines	Ethylenediamines	Phenothiazines	Piperidine	Piperazines
First generation					
Chlorpheniramine Tripolidine*	Diphenhydramine[§] Doxylamine[§**]	Antazoline[##] Mepyramine[II]	Promethazine	Cyproheptadine[#]	Buclizine Cyclizine** Hydroxyzine
Second generation					
				Desloratadine Ebastine Fexofenadine Levocabastine[##] Loratadine Mizolastine	Cetirizine Levocetirizine

*Available in combination preparations; [§]Used for sedative properties; **Used for nausea and vomiting; [#]Used as an appetite stimulant due to marked antiserotonergic activity; [##]Ophthalmic; [II]Parenteral (IM, IV)

Table IV: Comparing first- and second-generation H_1-receptor antagonists[25]

First generation	Second generation
Usually administered three to four times per day	Usually administered in a once or twice daily dose
Lipophilic; low molecular weight – cross the blood-brain barrier	Lipophobic; high molecular weight – do not cross the blood-brain barrier
Increased potential to cause side-effects e.g. sedation, convulsions, hyperactivity (refer to Figure 5)	Does not cause relevant side-effects in the absence of drug interactions
Reports of toxicity previously published	No reports of serious toxicity
Randomised, double-blind, placebo-controlled trials lacking in children	Some randomised, double-blind, placebo-controlled studies in children available
Lethal dose identified for infants/young children	No fatality due to overdose

Table V: Pharmacologic properties of oral H_1-receptor antagonists used in allergic disease[25]

Antihistamine	Onset of action	Hepatic metabolism	Interactions	Half-life
First generation				
Chlorphenamine maleate (e.g. Allergex®; Rhineton®)	30–60 minutes	Yes (CYP2D6)	Alcohol, CNS depressants, tricyclic antidepressants, anticholinergics, medicines affecting CYP2D6 enzymes	12–15 hours
Hydroxyzine HCl (e.g. Aterax®)	2 hours	Yes		16–24 hours
Prometazine HCl (e.g. Phenergan®; Lenazine®)	20 minutes	Yes		10-14 hours
Second generation				
Cetirizine HCl (e.g. Zyrtec®; Allecet®; Texa®)	1–3 hours	Yes, < 40%	Improbable	10 hours
Desloratadine (e.g. Deselex®; Dazit®, Pollentyme ND®)	2 hours	Yes (CYP3A4; CYP2D6)	Improbable	27 hours
Ebastine (e.g. Kestine®)	2 hours	Yes (CYP3A4)	Possible	15–19 hours
Fexofenadine HCl* (e.g. Telfast®; Tellerge®)	2 hours	Minimal, < 8%	Improbable	14 hours
Levocetirizine HCl (e.g. Xyzal®; Allerway 5; Levogex®)		Minimal, < 15%	Improbable	8 hours
Loratadine (e.g. Clarityne®; Clarinese®, Pollentyme®)	1–3 hours	Yes (CYP3A4; CYP2D6)	Improbable	12–15 hours
Mizolastine (e.g. Mizollen®)	1 hour	Yes (glucuronidation and minor CYP3A4; CYP2D6)	Possible	12.9 hours

*Terfenadine has been discontinued due to serious cardiac side-effects and superseded by fexofenadine HCl.

The H_1-receptor antagonists are divided into first- and second-generation agents. The first generation antihistamines have the ability to cross the blood-brain barrier,[24] cause sedation and are also more likely to block autonomic receptors (alpha- and muscarinic receptors).[22] The second-generation antihistamines are less lipid-soluble and are substrates of P-glycoprotein transporter in the blood-brain barrier; as a result these agents enter the central nervous system with difficulty or not at all.[22]

The route of administration is either systemic (oral; parenteral), or topical (intranasal; ophthalmic).[24] Absorption is rapid after oral administration with peak blood concentrations occurring in one to two hours. Some are extensively metabolised, mainly by microsomal systems in the liver. The active metabolites of hydroxyzine (cetirizine), terfenadine (fexofenadine), and loratadine (desloratadine) are available as medicines. The enzyme CYP3A4 metabolises several of the second generation antihistamines, posing important interactions between agents.[22]

Points to ponder

Diphenhydramine, hydroxyzine and promethazine are the most sedating antihistamines. Chlorphenamine is less sedating compared to other first-generation agents. Meclizine (the parent medicine is cyclizine), diphenhydramine, hydroxyzine, and promethazine have higher antiemetic activity than other antihistamines. Although second-generation antihistamines do not cause substantial sedation, cetirizine is more likely to do so when compared to the other agents in this class.[26]

Pruritus is troublesome in patients suffering from atopic dermatitis or eczema. Histamine is however only one of the mediators to cause pruritus and the older generation antihistamines are indicated at bedtime due to their sedative effects. Second generation H_1-receptor antagonists have been ineffective in controlling pruritus in this condition and should not be used in the treatment of eczema.[25]

Second-generation H_1-receptor antagonists are the only medicines with evidence in the treatment of chronic urticaria due to randomised prospective, double-blind and placebo-controlled studies. H_1-receptor antagonists are first-line symptomatic treatment of chronic urticaria.[25]

Conclusion

The management of Type 1 allergic conditions can be effectively managed with antihistamines. Of the two available classes, one of the newer second-generation agents is an appropriate choice as it has fewer side-effects and a better safety profile. Detailed knowledge of the available antihistamines is necessary so as to individualise therapy.

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