Antihistamines and allergies – an update

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Abstract

Allergic conditions are increasing globally. The most frequently occurring allergic conditions include atopic dermatitis, allergic rhinitis and asthma. Allergic reactions are immune-mediated and associated with considerable morbidity that impacts on quality of life and poses a socio-economic burden. It is therefore important to identify triggers and to understand the role of the complex immune system. Antihistamines are the most commonly prescribed medicines to treat allergies. Although the efficacy of H_1-receptor antagonists is very similar, their pharmacological properties differ and literature suggests that second generation H_1 antihistamines are the preferred treatment option. As a custodian of medicine, the pharmacist should have a good understanding of an allergic reaction, how to treat it appropriately and 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, the fifth leading chronic disease group across the globe.[1] The prevalence of allergy has risen significantly in the past few decades and is reported to have a worldwide incidence of 30–40%. Children are more prone to allergies than adults.[2] A comprehensive survey conducted worldwide (ISAAC Phase III) concluded that every third child below the age of 18 years, is allergic to some type of allergen.[3] A nationwide, prospective cohort study conducted in Korea over a period of six years also revealed that there is still a continued increase in prevalence in children diagnosed with atopic conditions.[4] The symptoms of asthma, allergic rhinitis and atopic eczema have also been seen to increase over the years in the adolescent population of Africa.[5]

In South Africa the exposure to allergens varies between rural and urban areas.[6] 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.[6,7] 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. This refers to the increased sensitivity of immunoglobulin E (IgE) to a specific antigen, which upon exposure to an allergen, results in a hypersensitivity response.[8-10] Atopic individuals are genetically predisposed to develop one or more allergic disorder, including certain food allergies. It has a strong familial link[2] – if both parents are atopic, the child has a 50% chance of suffering from an allergic disorder.[11] 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.[12]

Allergies can decrease quality of life, lead to absenteeism from school or the workplace, cause significant morbidity and even mortality, and furthermore pose a huge health cost.[1,7] It is therefore important to understand this disorder and treat it appropriately. In practice, the majority of diagnoses are made with a combination of supportive patient medical history and positive allergy tests, facilitated by more distinctive diagnostic cut-off points for specific IgEs and skin-prick tests.[10] Both non-pharmacological (e.g. allergen avoidance) and pharmacological strategies can be used in the prevention and management of allergic disease.[11]

The atopic march and risk factors for developing atopy

Different atopic diseases develop at certain ages during childhood. The atopic march refers to the sequence in which atopic diseases and their clinical symptoms manifest themselves as a child grows

Atopic dermatitis	Chronic disease, strongly linked to genetic predisposing factors, often resulting in skin barrier dysfunction, which establishes the basis for inflammatory responses, leading to dermatitis. It can also easily be aggravated by exposure to predisposing allergens, like pollen and various foods.[10]
Allergic rhinitis	Occurs due to inflammation of the epithelial lining of the nasal mucosa. The inflammatory process is initiated by the release of histamine owing to the cross-linkage of IgE antibodies with the mast cells, which in turn release histamine and other chemokines.[2] In addition, an array of early phase pro-inflammatory molecules is synthesised and released, causing oedema and fluid secretion, which may result in congestion and other nasal symptoms.[13-15]
Asthma	Chronic inflammatory disease which causes hyperresponsiveness of the bronchial tree, with reversible airflow obstruction. Pathological components include inflammation of the airway, contraction of the smooth muscle with resulting airway constriction, hypersecretion of mucus and bronchial hyperresponsiveness.[16,17]

Figure 1. The atopic triad[2,10,13-17]

older.[8,9] Pertaining to the atopic triad, atopic dermatitis often presents as the most common starting point for subsequent allergic diseases. Conditions of the respiratory tract, such as allergic rhinitis and asthma, subsequently develop with some clinical signs becoming more prominent while others subside.[12]

Various predisposing risk factors have been linked to the initial development of atopy. These risk factors include a genetic predisposition, obesity, allergen exposure, tobacco smoke, air pollutants, maternal weight gain or obesity, maternal use of antibiotics, maternal stress and decreased exposure to infections and endotoxins (the hygiene hypothesis).[8-10]

The immune system and sensitisation

A complex but vital network of cells and lymphoid organs makes up the immune system.[18] It is a highly interactive network, which responds on the basis of all body tissues, infections, normal flora bacteria, and various environmental agents.[19] 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.[20]

Acquired (adaptive) immunity requires prior exposure to an antigen and thus takes time to develop after the initial encounter with a new invader.[21]

The immune response in allergy begins with sensitisation.[22] All immune cells originate as immature stem cells in the bone marrow. They respond to cell signalling molecules (cytokines e.g. 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

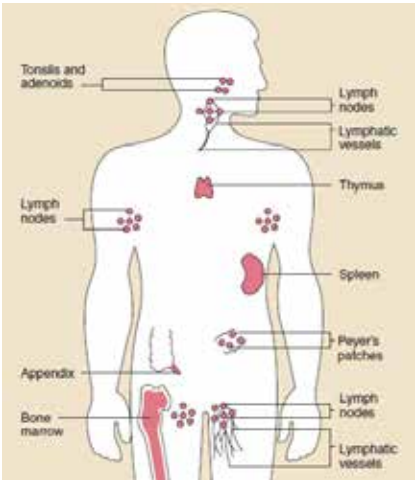

Figure 2. Lymphoid organs[20]

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.[20] 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.[23] 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.[24] 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.[25]

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.[20] 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.[22] The allergen-specific receptor site is now available for future interaction with the allergen.

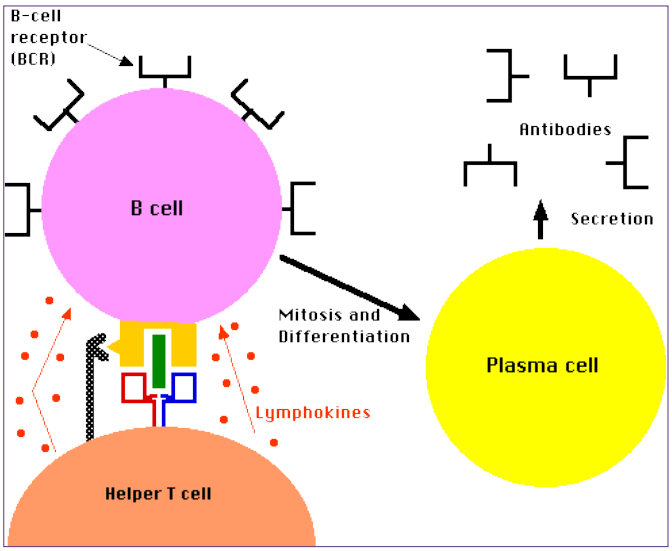

Figure 3. Specific immune cells[26]

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.[22] This leads to degranulation of cells and a subsequent release of a variety of preformed inflammatory mediators e.g. histamine, tumour 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.[27] 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 haematopoietic cells that express the c-Kit receptor.[27] Mast cells express high-affinity receptors (FcεRI) on their surface and attempt to sustain a fixed number of these receptors unoccupied.[27] 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.[22]

Early and late phase allergic reactions

The early phase reaction (immediate hypersensitivity) occurs within minutes of exposure to the allergen. The late phase reaction

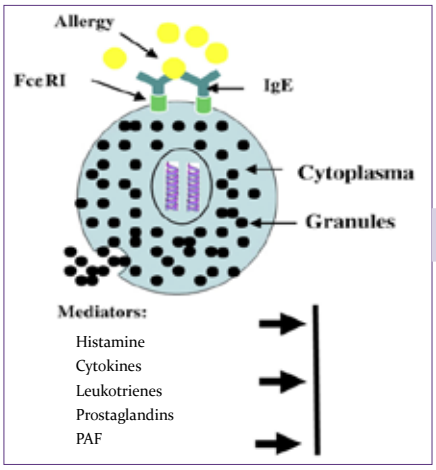

Figure 4. Activated mast cells[27]

Gastrointestinal tract	Airways	Blood vessels
Increased fluid secretion Increased peristalsis	Bronchoconstriction Increased mucus secretion	Vasodilation Increased permeability
Diarrhoea Vomiting	Wheezing, coughing, phlegm; swelling and mucus secretion in nasal passages	Oedema and increased flow of lymph to lymph nodes; increased cells and protein in tissues

Figure 5. Different effects on various tissues after mast cell activation[1]

occurs four to six hours after the symptoms of the early phase have subsided and can last for days or weeks.[22] 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.[23] A Type I allergy is evident within five to fifteen minutes after allergen exposure and therefore referred to as an immediate hypersensitivity.[29] Symptoms experienced by the patient vary and depend on the route of entry as well as the dose of the allergen.[1]

Table I. Classification of allergy[28]

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 immunity)
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[1], asthma, allergic rhinoconjuctivitis, anaphylaxis	Haemolytic anaemia, bullous pemphigoid, idiopathic thrombocytopaenia	Cutaneous small-vessel vasculitis, serum sickness, glomerulonephritis	Contact dermatitis

[1]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 mucus production Airway inflammation
Food allergy	Tree nuts Peanuts Shellfish Milk Eggs Fish	Oral	Vomiting Diarrhoea Pruritus Urticaria Anaphylaxis (rarely)

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).[23] These mediators are rapidly released into the extracellular environment and are responsible for many of the acute signs and symptoms of allergic reactions.[30]

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.[31]

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.[31]
- The effects mediated through the H_2 receptor: increased vascular permeability, increased gastric acid secretion, and airway mucus production, but 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.[30]

Non-pharmacological prevention and management

Table III provides an overview of prevention strategies which should be combined with more specific management principles according to the type of atopy that a patient is experiencing.[16,17]

Table III. Prevention strategies in the management of allergic diseases[16,17]

Prevention strategies in the management of allergic diseases
Early breastfeeding
Regular physical exercise
Probiotic bacteria may be anti-inflammatory
A healthy diet
Do not smoke around children
Avoid unnecessary use of antibiotics

A patient's immune tolerance may be improved by these strategies, however, the benefit of probiotics in the management (prevention and treatment) of allergic conditions remains inconclusive. Furthermore, several behavioural activities have been shown to provide some alleviation of the symptoms derived from a current allergic reaction,[33] but where non-pharmacological strategies do not alleviate the allergic condition, pharmacological agents may be used for the management thereof.[32]

Antihistamines as pharmacological management

The goal of therapy is to relieve symptoms and prevent severe reaction. Antihistamines are of value in the treatment of conditions such as allergic rhinitis, allergic conjunctivitis and chronic urticaria.[34] These agents block the actions of histamine by reversible competitive binding to H_1 receptors, thereby reducing histamine-mediated responses.[31] 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.[35] In the treatment of atopic dermatitis (eczema), antihistamines e.g. diphenhydramine are used primarily for the sedative effect to reduce awareness of itching.[31]

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,[35] cause sedation and are also more likely to block autonomic receptors (alpha- and muscarinic receptors).[31] 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.[31]

Table V. Comparing first and second generation H1-receptor antagonists[36]

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

The route of administration is either systemic (oral; parenteral), or topical (intranasal; ophthalmic).[35] 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.[31]

Table IV. Chemical classification of H1-receptor antagonists[34, 36]

Alkylamines	Ethanolamines	Ethylenediamines	Phenothiazines	Piperidine	Piperazines
First generation					
Chlorpheniramine Tripolidine*	Diphenhydramine§ Doxylamine§**	Antazoline## Mepyramine‖	Promethazine	Cyproheptadine#	Buclizine Cyclizine** Hydroxyzine
Second generation					
				Desloratadine Ebastine Fexofenadine Levocabastine## Loratadine Mizolastine Rupatadine	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; ‖Parenteral (IM, IV)

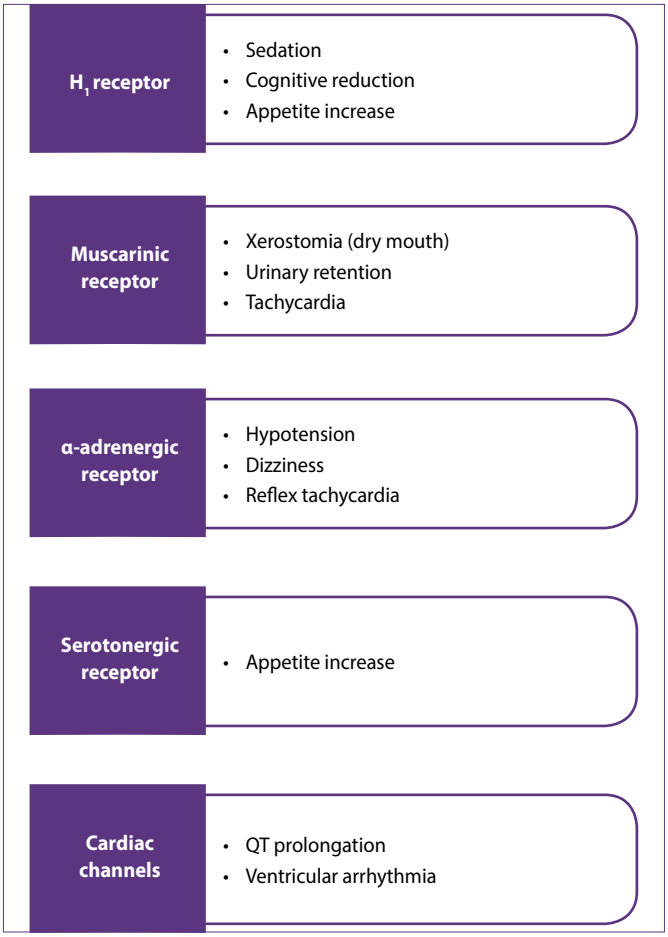

Figure 6. Adverse effects of first generation H_1-receptor antagonists[36]

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.[39]
- 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 the control of pruritus in this condition and should not be used in the treatment of eczema.[36]
- 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.[36] A newly-launched long-acting H_1-receptor antagonist and PAF receptor inhibitor, rupatadine fumarate, is non-sedating and approved for the treatment of chronic urticaria and allergic rhinitis in adults and children 12 years of age or older. This agent inhibits the degranulation of mast cells and the subsequent release of cytokines, more specifically of TNF-α found in the mast cells, as well as monocytes. Rupatadine fumarate's approved dosage is 10 mg daily.[37,40]

Table VI. Pharmacologic properties of oral H_1-receptor antagonists used in allergic disease[36,37,38]

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®)	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®)		Minimal, < 15%	Improbable	8 hours
Loratadine (e.g. Clarityne®; Clarinese®)	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
Rupatadine fumarate (Rupanase 10®)	30 minutes	Yes	Ketoconazole, erythromycin, or any other potential CYP3A4 inhibitor	5.9 hours

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

Conclusion

The atopic march underlies the pathophysiologic manifestations of atopy-related conditions, such as atopic dermatitis, allergic rhinitis and asthma. The management of Type 1 allergic conditions can be effectively managed with antihistamines. Of the two available classes, currently, a newer second-generation agent is considered to be the mainstay of treatment for allergic disease, as it has fewer side-effects and a better safety profile than the first-generation H_1-antihistamines. Detailed knowledge of the available antihistamines is necessary so as to individualise therapy.

References

1. Janeway CA Jr, Travers P, Walport M, et al. Immunobiology: The immune system in health and disease. 5th ed. New York: Garland Science. 2001. http://www.ncbi.nlm.nih.gov (Accessed 18/08/2016).
2. Kumar Y, Bhatia A. Immunopathogenesis of allergic disorders: current concepts. Expert Rev Clin Immunol. 2013;9(3):211-216. http://www.medscape.com (Accessed15/08/2016).
3. Asher MI, Montefort S, Björkstén B, et al. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjuctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368(9537), 733-743(2006).
4. Kim B, Kim J, Kang M, et al. Allergies are still on the rise? A 6-year nationwide population-based study in Korea. Allergology International. 2016;65(2):196-191.
5. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. Pediatr Allergy Immunol. 2007;18:560-565.
6. Mbugi EV, Chilongola JO. Allergic disorders in Africa and Africans: is it primarily a priority? WAO Journal 2010;3:175-181.
7. Okada H, Kuhn C, Feillet, Bach JF. The "hygiene hypothesis" for autoimmune and allergic diseases: an update. Clin Exp Immunol 2010;160:1-9.
8. Van der Poel L, Warner J. Paediatric allergy in review. Paediatrics and Child Health. 2012;22(7):259-263.
9. Leyva-Castillo J, Li M. Thymic stromal lymphopoietin and atopic diseases. Revue Francaise d'Allergologie. 2014;54(5):364-376.
10. Bieber T. Atopic dermatitis. Ann Dermatol. 2010;22(2):125-137.
11. Asthma and Allergy Foundation of America. http://www.aafa.org/page/allergy-treatments.aspx (Accessed 17/08/2016).
12. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003; 112(Suppl.6):S118-27. http;//dx.doi.org/10.1016/j.jaci.2003.09.033. http://www.ncbi.nlm.nih.gov/pubmed/14657842 (Accessed 15/08/2016).
13. Schad CA, Skoner DP. Antihistamines in the pediatric population: achieving optimal outcomes when treating seasonal allergic rhinitis and chronic urticaria. Allergy and Asthma Proceedings. 2009;29(1):7-13.
14. Ciprandi G, Cirillo I, Pistorio A. Persistent allergic rhinitis includes different pathophysiologic types. Laryngoscope. 2009;119:395-399.
15. Cox L, Calderon MA. Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of treatment practices in the US and Europe. Current Medical Research and Opinion. 2010;26(12):2723-2733.
16. Global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention. 2014. Available at: www.ginasthma.Org (Accessed 08/09/2017).
17. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. The Lancet. 2010;376:903-913. Available at: http://www.sciencedirect. com/science/article/pii/S0140673610610972# (Accessed 08/09/2017).
18. Allergies and the immune system. http://www.hopkinsmedicine.org (Accessed 18/08/2016).
19. Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. J Allergy Clin Immunol. 2009;123(4):735-746.
20. Understanding the immune system. How it works. National Institute of Allergy and Infectious Diseases. 2003. http//www.niaid.nih.gov (Accessed 18/08/2016).
21. Delves PJ. Overview of the immune system. http//www.merckmanuals.com/professional/immunology-allergic-disorders (Accessed 19/08/2016).
22. Portnoy J. IgE in clinical allergy and allergy diagnosis. 2003. http://www.worldallergy.org/professional/allergic_diseases_center (Accessed 16/08/2016).
23. Buelow B. Immediate hypersensitivity reactions. 2015. http://emedicine.medscape.com/article/136217-overview (Accessed 15/08/2016).
24. Cytokines and immunoregulation. http://www.microbiologybook.org/mobile/m.immuno-13.htm (Accessed 18/08/2016).
25. Ngoc LP, Gold DR, Tzianabos AQ, et al. Cytokines, allergy, and asthma. Current Opinion in Allergy and Clin Immunol. 2005; 5(2):161-166. http://ovidsp.tx.ovid.com/sp-3.21.0a (Accessed 22/08/2016).
26. B cells and T cells. http://www.biology-pages.info/B/B_and_Tcells.html (Accessed19/08/2016).
27. Amin K. The role of mast cells in allergic inflammation. Respir Med. 2012;106:9-14.
28. Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: a re-interpretation. Trend in Immunology. 2003;24(7):376-379.
29. Immunity, allergic reactions. http://www.derm-hokadai.jp/shimizu-dermatology/pdf/03-03.pdf (Accessed 17/08/2016).
30. Gurish M, Castells MC. Mast cell derived mediators. http://www.uptodate.com (Accessed 19/08/2016).
31. Katzung BG, Masters SB, Trevor AJ. Basic and Clinical Pharmacology. 11th ed. 2009; 271-292. Singapore: McGraw-Hill.
32. Nathan RA. The pathophysiology, clinical impact, and management of nasal congestion in allergic rhinitis. Clinical Therapeutics. 2009;30(4):573-594.
33. Naclerio RM, Bachert C, Baraniuk JN. Pathophysiology of nasal congestion. International Journal of General Medicine. 2010;3:47-57.
34. Rossiter D, editor. South African Medicine Formulary. 12th ed, Cape Town: Health and Medical Publishing Group. 2016.
35. Schellack N, Schellack G, Janse van Rensburg M. An overview of anti-allergic drug therapy and the histamine-1 antihistamines. SA Fam Pract 2015;57(1):43-49.
36. Criado PR, Criado RFJ, Maruta CW, Filho Cd'AM. Histamine, histamine receptors and antihistamines: new concepts. An Bras Dermatol. 2010;85(2):195-210. http://www.scielo.br/pdf/abd/v85n2/en_10.pdf (Accessed 21/08/2016).
37. Shamizadeh S, Brockow K, and Ring J. Rupatadine: efficacy and safety of a non-sedating antihistamine with PAF-antagonist effects. Allergo J Int. 2014; 23(3): 87–95.
38. Drug Monograph. Rupatadine. http://accesspharmacy.mhmedical.com/drugs (Accessed 12/10/2017)
39. Brenner GM and Stevens CW. Pharmacology. 4th ed. 2013; 274-283 Philadelphia: Elsevier Saunders.
40. Mullol J, Bousquet J, Bachert C, et al. Rupatadine in allergic rhinitis and chronic urticaria. Allergy.2009; 63 Suppl 97:5–29.