A COMPARATIVE STUDY ON THE EFFICACY OF ISOTONIC AND HYPOTONIC INTRANASAL CORTICOSTEROID SPRAY IN ALLERGIC RHINITIS

By

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List of abbreviations

APC	- Antigen Presenting Cell
AR	- Allergic Rhinitis
ARIA	- Allergic Rhinitis and its Impact on Asthma
ECP	- Eosinophil cationic protein
GM-CSF	- Granulocyte-macrophage colony stimulating factor
IgE	- Immunoglobulin E
IL-4	- Interleukin-4
INSs	- Intranasal Corticosteroid Spray
MLK	- Modified Lund-Kennedy
NAR	- Non-allergic rhinitis
RAST	- Radioallergosorbent Test
SNOT-22	- Sinonasal Outcome Test - 22
SPT	- Skin Prick Test
TNSS	- Total Nasal Symptom Score

Abstract in Bahasa Melayu

Pengenalan: Semburan hidung corticosteroid adalah salah satu rawatan yang paling berkesan dalam penyakit resdung. Terdapat pelbagai jenis semburan hidung corticosteroid di Malaysia. Walaupun bahan utama dalam semburan hidung adalah produk berasaskan steroid, perbezaan kepekatan boleh memberikan kesan yang berbeza dalam mengawal gejala alahan resdung. Pertimbangan dalam kepekatan adalah penting bagi penyedian ubatan dan boleh mempengaruhi penyerapan, pengekalan dan seterusnya keberkesanan serta keselamatan ubat.

Objektif: Kajian ini dijalankan untuk menentukan keberkesanan jenis semburan hidung dalam merawat resdung dengan membandingkan keberkesanan menggunakan beberapa parameter klinikal iaitu; TNSS, SNOT-22 dan pemeriksaan nasoendoskopik 'Modified Lund-Kennedy'. Keberkesanan juga ditentukan dengan menguji penanda radang alahan seperti serum Interleukin-4 dan kiraan eosinofil dalam darah.

Kaedah: Kajian Perbandingan Intervensi, label terbuka yang melibatkan 2 kumpulan (kumpulan semburan hidung hipotonik dan kumpulan semburan hidung isotonik) telah dijalankan di klinik Otorinolaringologi Hospital Sultanah Nur Zahirah Kuala Terengganu dan Klinik Otorinolaringologi Hospital Universiti Sains Malaysia Kubang Kerian Kelantan bermula dari Jun 2015 hingga Mei 2016. Kajian melibatkan pesakit luar yang berumur dari 18-70 tahun, yang dirawat di klinik dan disahkan menghidap resdung berdasarkan gejala dan telah bersetuju untuk ujian *'skin prick test'*.

Keputusan: Statistik ANOVA digunakan untuk melihat keberkesanan di antara semburan hidung isotonik dan hipotonik yang meliputi 'Total Nasal Symptom Score (TNSS)', 'Sinonasal Outcome Test–22(SNOT-22)' dan pemeriksaan nasoendoskopik 'Modified Lund-Kennedy'. Hanya pemeriksaan nasoendoskopik 'Modified Lund-Kennedy' menunjukkan perbezaan di antara kedua-dua kumpulan ini, F = -2.23, $\boldsymbol{p = 0.026}$. Ujian Mann Whitney

digunakan dimana median (IQR) untuk semburan hidung hipotonik = 3.00 (4.00) dan semburan hidung isotonic = 2.00 (4.00). Bagi penilaian makmal, keberkesanan antara kedua-dua kaedah semburan dianalisa menggunakan statistik *t*-test. Untuk ujian IL-4, perbezaan min antara semburan hidung isotonik dan hipotonik adalah tidak signifikan (p = 0.337, 95% CI-0.91, 0.32). Keputusan ujian kiraan eosinofil juga menunjukkan tidak signifikan (p = 0.190, 95%CI -0.38, 0.08).

Rumusan: Tidak banyak perbezaan keberkesanan antara semburan hidung isotonik dan hipotonik menggunakan parameter klinikal dan penilaian makmal. Dalam kajian ini, hanya pemeriksaan nasoendoskopik 'Modified Lund-Kennedy' menunjukkan statistik signifikan menggunakan semburan hidung isotonik. Sebagai rumusan, semburan hidung isotonik menunjukkan hanya sedikit kelebihan dari semburan hidung hipotonik dalam mengawal gejala alahan resdung.

Abstract in English

Background: Intranasal corticosteroid spray is one of the most effective treatment in allergic rhinitis. There are various types of intranasal corticosteroid spray available in Malaysia. Although the main ingredient in nasal spray is steroid-based products, the difference of tonicity could show different effect in controlling the symptoms of allergic rhinitis. Tonicity is an important consideration for drug formulation and can affect its uptake, retention and consequent efficacy and safety.

Objective: This comparison study is to determine the efficacy of different type of nasal spray in treatment of allergic rhinitis by comparing the efficacy using several clinical parameters that are Total Nasal Symptom Score (TNSS), Sinonasal Outcome Test Score-22 (SNOT-22) and Modified Lund-Kennedy (MLK) nasoendoscopic examination. Efficacy is also determined with allergy inflammatory markers such as serum Interleukin-4 and blood eosinophilic count.

Methods: Comparative interventional study, open label involving 2 groups (hypotonic nasal spray group and isotonic nasal spray group) was carried out in Otorhinolaryngology Clinic of Hospital Sultanah Nur Zahirah Kuala Terengganu and Otorhinolaryngology Clinic of Hospital Universiti Sains Malaysia Kubang Kerian Kelantan commencing from June 2015 till May 2016. Study involves walk-in patient aged from 18-70 years old, who are seen in clinic from this two centres that are diagnosed with allergic rhinitis based on symptom and sign and had consented for skin prick test.

Results: ANOVA test was applied to study the efficacy of isotonic and hypotonic nasal spray which includes TNSS, SNOT-22 and Modified Lund-Kennedy nasoendoscopic examination score. Only Modified Lund-Kennedy nasoendoscopic score showed significant difference between the two groups, F = -2.23, ***p* = 0.026**. Mann Whitney test was applied, median (IQR) for hypotonic spray =3.00(4.00) and isotonic spray 2.00(4.00). For inflammatory markers, effects of both method were analysed by using *t*-test. For IL-4, the difference between the mean isotonic and hypotonic nasal spray was not statistically significant (p = 0.337, 95% CI-0.91, 0.32). Same findings were demonstrated in eosinophil counts which showed no statistically different (p = 0.190, 95%CI -0.38, 0.08).

Conclusions: There is not much difference on the efficacy between isotonic and hypotonic using clinical parameters and allergic inflammatory markers. The only significant findings in this study is by using the Modified Lund-Kennedy nasoendoscopic score which shows improvement with isotonic nasal spray. As a conclusion, isotonic INSs has a slightly superior efficacy than hypotonic INSs for treatment of AR in reducing the signs and symptoms.

CHAPTER 1: INTRODUCTION

Allergic rhinitis (AR) is a common hypersensitivity reaction that affect our community and worldwide. It is a disease of inflammatory reaction in the nasal mucosa due to immunological response towards offending allergen. The inflammatory reactions occur due to hypersensitivity of nasal mucosa through immunoglobulin E (IgE) mediated antibodies which is also well known as hypersensitivity type 1 (Skoner, 2001). The prevalence of AR is increasing and has become a major health problem in many countries. Although it is not associated with direct mortality, it carries a significant morbidity and has a huge socioeconomic burden. It may impacts quality of life of a patient such as poor productivity, lack of sleep and emotional disturbances. For school-age children with allergic rhinitis, they may miss school, had poor performance in classrooms and limit them in school activities.

Worldwide, it is estimated around about 400 million people suffer from AR (Pawankar et al., 2012). In Malaysia, prevalence of AR among Malaysian population was about 38%-40% (Ho et al., 2011) and AR among children is half that of the adult population which is about 27% (Quah et al., 2005). As it is a relatively common problem encountered in the community, various studies have been done to understand the disease better.

Management of AR is costly. In fact, a study done from 2001 to 2005 in England showed a 41.7% overall increase in prescriptions for antihistamines and drugs used in nasal allergy (Ghouri et al., 2008). It may also impact productivity of an organization due to miss work among workers which affect the economic growth. In the United States, AR results in 3.5 million lost workdays and 2 million lost schooldays annually. Patients often struggle to

alleviate their misery, by self-adjusting their treatment regimen using over-the-counter medications because of the lack of efficacy, deterioration of efficacy, lack of 24-hour relief, and bothersome side effects (Nathan, 2007).

Clinically, AR is characterized by 4 cardinal symptoms which are sneezing, rhinorrhoea, itchy nose and nasal blockage. These symptoms are aggravated when patient are exposed to allergen such as house dust mite, seafood, pollen and others. The most common aero-allergens like dust-mites, pollens and animal dander are responsible for many of the sensitivity reactions in allergic rhinitis.

Study of AR patients in Kelantan showed almost 50% of AR patients are due to seafood allergies, followed by chicken-based food. Of particular interest, among local Kelantanese most commonly induced seafood allergy was the anchovy sauce (Asha'ari et al., 2010).

The classification of AR can be intermittent or persistent and its severity can be either mild, moderate or severe as advocated by Allergic Rhinitis and its Impacts on Asthma (ARIA) Guidelines 2008 (Pawankar et al., 2012). The standard treatments of AR are avoidance of allergen, oral antihistamines and intranasal corticosteroid. Currently there are many available types of intranasal corticosteroid in the markets with mostly in isotonic solution. Since past few years, there is a new intranasal corticosteroid in the market which is hypotonic solution. It is believed to be more rapid and longer acting. There are many studies done comparing intranasal corticosteroid with placebo, but so far there is no study done to compare between isotonic and hypotonic intranasal corticosteroid spray.

Physiologically, tonicity is a property of a solution in reference to a particular membrane. In regards to cell tissue tonicity, it is the net osmolar gradient across the cell membrane. Tonicity is important for predicting the overall outcome of any changes in osmolality because it allows these solutes to cross the cell membrane in a tissue. Hence all tissue in human body is in osmotic equilibrium with each other. Movement of water across cell membranes occurs continuously until intracellular and extracellular tonicities are equal (Homer et al., 2000).

According to basic physiology tonicity of molecule, a solution is defined as a homogeneous mixture of two or more substances. One of the substances is called a solvent (a substance in which other substance or substances are dissolved). The substances dissolved in a solvent are called solutes (Rohrscheib et al., 2015).

- Isotonic solutions are two different solutions that have the same solute concentration.
- Hypertonic solution is two different solutions in which one solution has a higher solute concentration.
- Hypotonic solution is two different solutions in which one solute has a lower solute concentration.

Tonicity plays an important role in treating or reducing the clinical symptoms and signs of a disease. Theoretically, isotonic molecules will stay at the same tonicity with the nasal mucosa and it has tendency to dwell longer. In contrast, it was postulated that hypotonic molecules will have rapid absorption into the nasal mucosa compared to isotonic solution (Sato et al., 2007). This advantage can be utilized for pharmacology use in treating common problems in AR.

Various type of INSs with different preparation are currently available for the treatment AR. Different tonicity suspension may give different efficacy in alleviating symptoms of AR. Previous publication were mainly focus on comparison of existing INSs with placebo on the aspect of efficacy and safety. However, limited study were done to asses between different types of INSs in improvement of AR symptoms. Therefore this study can be a starting point to explore further in terms of clinical and laboratory data in patient with AR.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy and Physiology of the nose

Better understanding of the anatomy and physiology of the nose will help in the treatment of patient with AR. External nose is pyramidal in shape with its root up and the base is directed downward. This nasal pyramid is made of osteocartilagenous and membranous framework covered by skin (Figure 1). The upper one third of the external nose is bony while the lower one third is cartilaginous. The bony part consists of two nasal bones that meet in the midline and rest on the upper part of nasal process of the frontal bone. Laterally, these bones are held between the frontal processes of the maxilla. Whereas the cartilaginous part is consists of upper and lower lateral cartilage, lesser alar or sesamoid cartilages and septal cartilage that formed the nasal septum (Netter,2014)

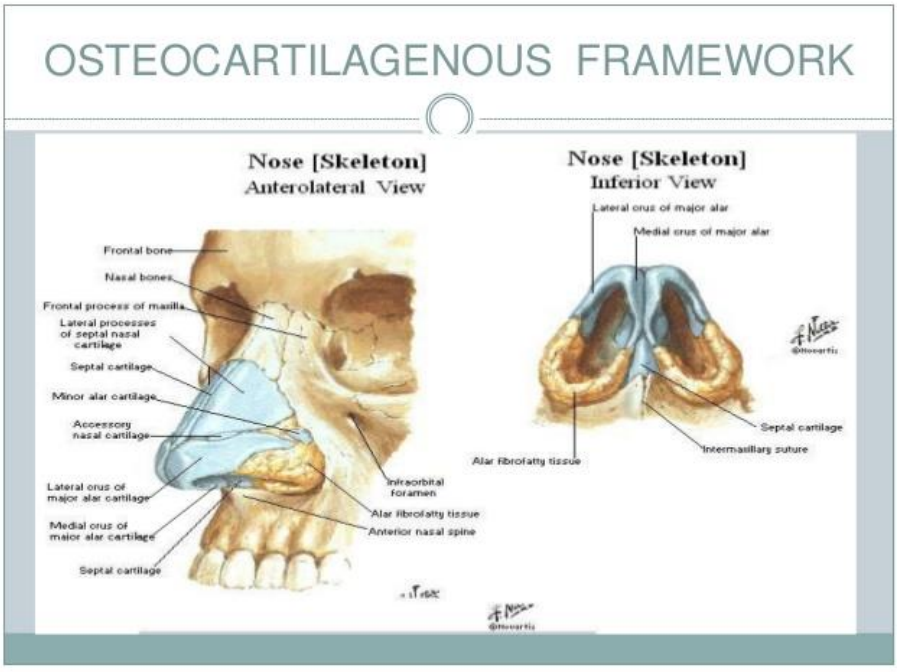

Figure 2.1 - Osteocartilagenous framework of nose
(Figure adapted from Neil S. Norton, Netter's Head and Neck Anatomy for Dentistry: Saunders Elsevier Inc 2007, 152)

Internal nose is divided into right and left cavities by the nasal septum. Each nasal cavity communicates with the exterior through nostril and with the nasopharynx through the posterior nasal aperture or the posterior choana. Each nasal cavity consists of skin-lined portion, the vestibule and a mucosa line portion, the nasal cavity proper. Vestibule is lined by skin and contains sebaceous glands, hair follicles and hair also known as vibrissae. Its upper limit on the lateral wall is marked by limen nasi which is formed by the caudal margin of upper lateral cartilage. Its medial wall is formed by the columella and lower part of the nasal septum up to its mucocutaneous junction(Netter, 2014).

Each nasal cavity is bounded with the lateral and medial wall, the roof and the floor. Medial wall is made up from the nasal septum. Lateral wall is formed by three scrolls like projections namely inferior, middle and superior turbinates (Figure 1). Below and lateral to each turbinate is the corresponding meatus. Each of the meatus has their own openings from the paranasal sinuses. In the inferior meatus, there is nasolacrimal ducts opening that drain the tears from the eyes into the nose and eventually get swallowed through the nasopharynx. Maxillary, frontal and anterior ethmoidal and sphenoid sinuses open into the middle meatus. The openings allow the drainage of mucus from correspond paranasal sinuses into the nasal cavity then into the nasopharynx. This process is regulated by the delicate and a well organized mucociliary clearance of nasal epithelium mucosa.

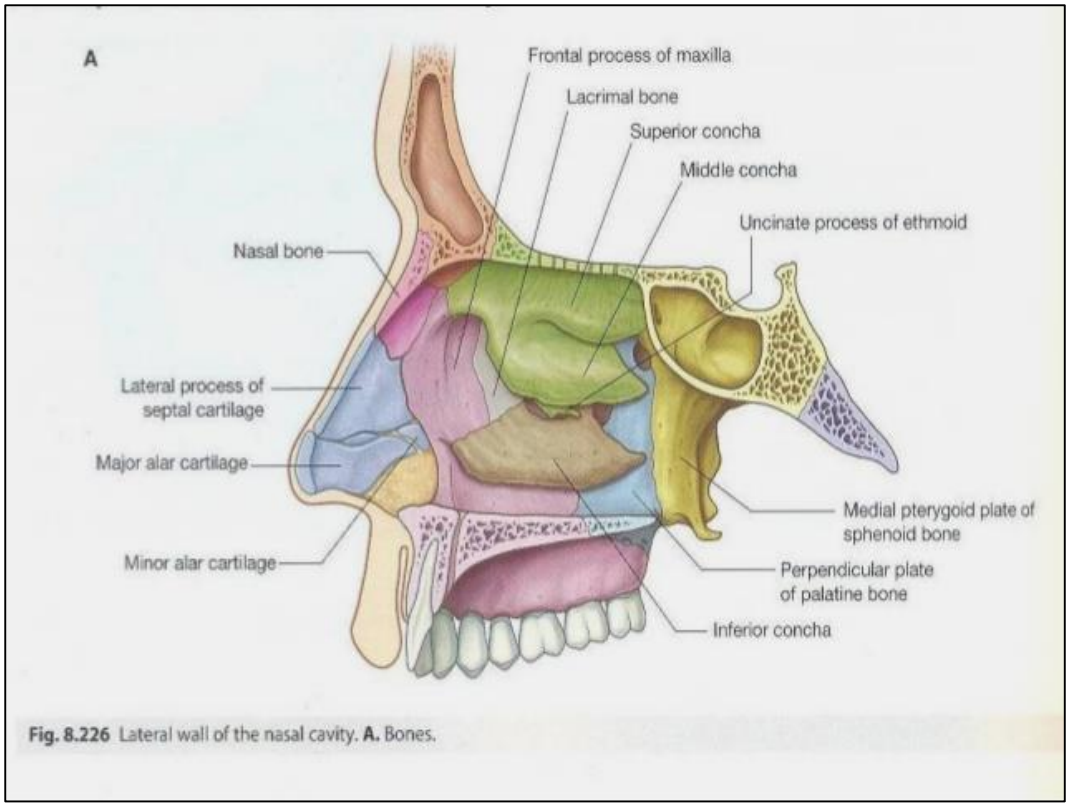

Figure 2. 1 - Lateral Wall of Nasal Cavity

(Figure adapted from Kirschner, Celeste G. Netter's Atlas of Human Anatomy Elsevier Inc 2005, Chapter: Head and Neck Page: 30)

The nasal cavity is generally lined by the pseudostratified ciliated columnar epithelium which contains goblet cells except at the roof. Approximately one to two centimetres from the cribriform plate and its corresponding lateral wall is lined by olfactory epithelium that contains olfactory receptors which is responsible for smell. The respiratory epithelium that lines the majority of the nasal cavity are responsible for humidification and warming the air, filtering the air from foreign particles and killing microbes via the mucus that they produced which contain plenty of enzymes and antibodies in it (Costanzo, 2014).

The nose is the primary organ of smell and part of the respiratory system. Apart from that, the nose is the one of important organ that functions in sensing smell. There are other several interesting functions of the nose (Table 2.1)

Table 2.1: Physiological Functions of the Nose (adapted from Scott-Brown's Otorhinolaryngology, Head and Neck Surgery 7th edition)

Function	**Mechanism**
a) Respiration	
• Heat exchange	• Direction of blood flow, evaporation heat
• Humidification	• Capillary permeability
• Filtration	• Laminar/turbulent flow
• Nasal resistance	• Anatomical and neurovascular
• Nasal fluid and ciliary functions	• Mucus, mucins
• Nasal neurovascular reflexes	• Sympathetic or parasympathetic
b) Voice modification	Nasal escapes
c) Olfaction	Perceived smell through pathways to higher centres

2.3 Definition of Rhinitis

Rhinitis is defined as an inflammatory condition of the nasal mucosa characterized by four cardinal symptoms which are sneezing, rhinorhea, itchiness and nasal blockage. There are many classification of rhinitis such as perennial or seasonal, allergic or non-allergic and intrinsic or extrinsic allergic rhinitis (Small and Kim, 2011).

Previous studies classified AR as seasonal or perennial, according to the occurrence of symptoms during the year and the type of allergen. Typically, seasonal AR is caused by a variety of outdoor allergens, mainly pollen, whereas perennial AR is mostly related to indoor allergens, such as house dust mite, pets, and cockroaches. The distinction between seasonal and perennial AR, however, is not applicable to all patients (e.g., concomitant sensitization to indoor- and outdoor allergens) and in all countries (e.g. perennial occurrence of pollen). The general classification of AR, therefore, has been revised by the ARIA (Allergic Rhinitis and its Impact on Asthma) workshop group, a World Health Organization initiative. Based on duration of symptoms, ARIA classifies AR as ‘intermittent’ or ‘persistent’ and depending on the impact of the disease on quality of life or daily activities into ‘mild’ or ‘moderate/severe’. It was recently suggested to label the latter category just ‘severe’ as the vast majority of patients in this ARIA category reported symptoms affecting two or more quality of life criteria such as daily activities, work, or sleep (Keil et al., 2010)

2.4 Epidemiology

AR is one of the most widespread chronic inflammatory diseases. Worldwide, the prevalence of allergic diseases such as AR and asthma are markedly increased to epidemic proportions. An estimated 300 million persons worldwide have asthma and about 400 million people suffer from AR. AR affects 10% to 20% of the general population in Europe and the United States of America (Ozdoganoglu and Songu, 2012). AR has a marked impact on quality of life, school absenteeism among school children, sick leave among workers and thus it causes huge socioeconomic burden to many countries (Pawankar et al., 2012). Furthermore, AR accounts up to 40% of children aged group, and it is associated with numerous complications and also been considered a risk factor for asthma (Berger, 2004).

The International Study of Asthma and Allergies in Childhood (ISAAC) Phases Three observed a rise in prevalence of asthma, allergic rhinoconjunctivitis and eczema after five years duration from ISAAC Phase One Study across Asia Pacific region (Asher et al., 2006). In the adolescent group, the Asia Pacific region was in the mid-range for reported symptoms of rhinoconjunctivitis at a global scale. However, the prevalence in Hong Kong and Bangkok were among the highest recorded worldwide. In the 6 to 7-year-old group, Asia Pacific had a fairly high prevalence of rhinoconjunctivitis ranked as the third highest region globally (Wong et al., 2013)

In South East Asia, the prevalence of allergic rhinitis differs between countries and even between areas within countries (Asher et al., 2006). These differences may partly be due to different definitions and methods used. Study done in Vietnam shows 50.2% of their

population are suffering from AR. Prevalence between urban and rural area showed considerably higher rates in urban compared to rural about 29.6% to 10.0% respectively (Lâm et al., 2011). In addition, allergic disorders are common in Singapore and prevalence is comparable to some populations in the West. The prevalence of AR was 44% in which are more common in higher socioeconomic status group (Goh et al., 1996).

House dust mites are the most common indoor allergens for allergic diseases such as AR and asthma. In tropical country with warm and humid climate, it has high prevalence of house dust mite. It is commonly found in association with bedding products, carpets, curtains and fabric products. Nowadays, lifestyle changes showed people spend more times often indoor that will increased exposure to indoor allergens. In Malaysia, there is increasing prevalence of AR and asthma with increased sensitivity towards house dust mite which is contributed by the improvement in socioeconomic status, westernized life styles and home environments conducive to proliferation of house dust mite(Sinniah and Thakachy, 2014).

Nevertheless AR affects both adult and a children group in many countries and it remains largely undiagnosed in certain region worldwide due to low socioeconomic condition as poor hygiene that lead to expose to an allergens as well as difficulty in medical access and lack of study research done.

2.5 Pathophysiology

The immune system of human's body has innate and adaptive response (Figure 2). The functions of the adaptive immune response are the recognition of specific "non-self" antigens or "self" antigens. The adaptive immune response regulates the generation of pathogen-specific immunologic effector pathways that eliminates specific pathogens or pathogen-infected cells. The cells of the adaptive immune system are T cells, which are activated through the action of antigen presenting cells (APC) and B cells (Liu et al., 2012).

Our immune system is continuously exposed to a wide variety of disturbances. Such disturbances are recognized by T cells via antigen presentation. Antigen presentation is a process in which antigen presenting cells (APC) capture the antigens, break them into small peptides, couple them with MHC molecules, and present them on the cell surface, thus enabling their recognition by T cells (Khailaie et al., 2013).

AR is a condition of an inflammation of the mucous membranes of the nose, paranasal sinuses, eyes, eustachian tubes, middle ear and pharynx. In certain people, other organs may also be affected. The inflammation of the mucous membranes is characterized by a complex immunological cascade releasing inflammatory mediators. This is triggered by immunoglobulin E (IgE) - mediated response to an extrinsic protein or polysaccharides which is called allergen. This inflammatory condition is described as hypersensitivity type 1 reaction (Warrington et al., 2011)

Hypersensitivity type 1 is characterized by local and systemic manifestation of Ig-E mediated hypersensitivity. It is a process of IgE-mediated inflammatory disease of the nasal mucous membranes due to the interaction of allergen characterized by an inflammatory infiltrate made up of eosinophils, T cells, mast cells and basophils, which release several mediators, chemokines and cytokines (among these, histamine and cysteinyl-leukotrienes are the major vasoactive mediators), regulation of the local and systemic IgE synthesis, and communication with the immune system and the bone marrow (Naclerio, 1991). AR patient can be allergic to inhalants (aeroallergen) and food allergen. However, aeroallergen can induce activation of mechanism of AR of early and late phase allergic reactions. After deposition and elution of allergens into the mucus layer, the allergens are taken up by antigen presenting cells and processed and presented to helper T lymphocytes. Activated helper T lymphocytes release cytokines like IL-4 and IL-13 and interact with B lymphocytes to induce the synthesis of allergen specific IgE. Thereafter, the allergen-specific IgE binds to the high affinity receptor for IgE on the surface of mast cells (Pawankar et al., 2011).

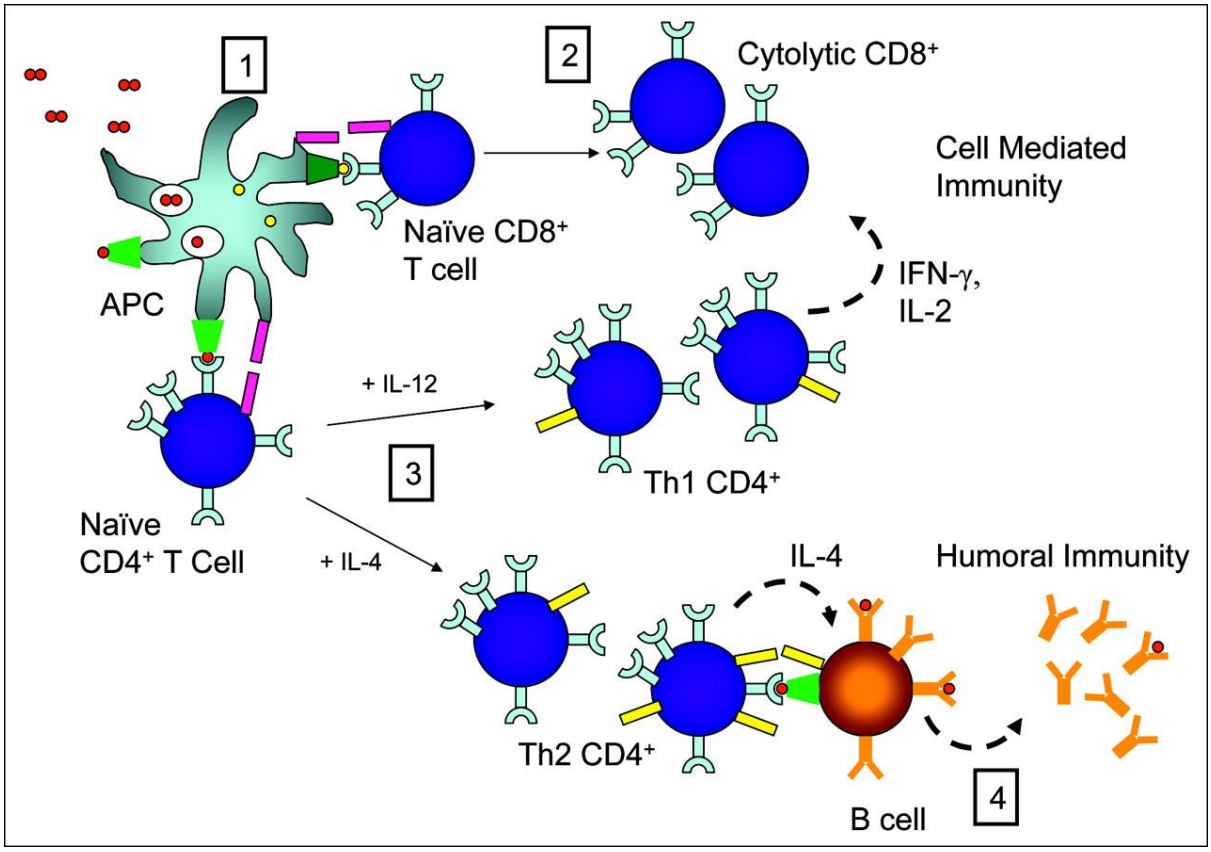

Figure 2.2 - Adaptive Immunity

(Adapted from figure of Neoreviews Vol. 6 No. 10 October 01, 2005, published online September 30, 2005 pp. e454-e462.doi: 10.1542/neo.6-10-e454)

Basically, pathophysiology of AR can be divided into 4 stages namely sensitization, early phase, late phase and systemic activation (Michael Gleeson, 2008). (Figure 2.2)

Sensitization

Once allergen such as grass pollen, house dust mite, cat dander are inhaled and deposited into the mucus layer which cannot be clear up by mucociliary clearance, the allergens are engulfed by antigen presenting cells (APC) such as dendritic cells called Langerhans cells. They are then processed and then presented to helper T lymphocytes. Activated helper T

lymphocytes release cytokines like IL-4, IL-5 and IL-13 and interact with B lymphocytes to induce the synthesis of allergen specific IgE. Thereafter, the allergen-specific IgE binds to the high affinity receptor for IgE on the surface of mast cells. A mast cell is a type of granulocyte derived from myeloid stem cell that plays a role in mediating allergic response and contains granules and chemical mediators such as histamine, cytokines, granulocyte macrophage colony-stimulating factor, leukotrienes, heparin and many proteases causing symptoms of allergy (Pawankar et al., 2011).

Early phase response

The early or immediate phase response occurs in sensitized individuals within minute of exposure to the same allergen and it lasts for about 2-3 hours. One of the cardinal components of the early phase response is the degranulation of mast cells. In the sensitized individual, mast cells are abundant in the epithelial compartment of the nasal mucosa and can be easily activated upon re-exposure to the allergens. Upon crosslinking of the allergen specific IgE bound to the surface of mast cells by the specific allergen, mast cells degranulate and release a variety of pre-formed and newly formed mediators leading to what is known as the early phase response (Klimek and Schendzielorz, 2008).

Histamine which is secreted by basophils and mast cells is the major mediator of AR, stimulates the sensory nerve endings of the trigeminal nerve and induces sneezing. Histamine also stimulates the mucous glands to secrete mucous causing rhinorrhoea. At the same time, histamine, leukotrienes and prostaglandins act together on the blood vessels causing congestion of nose (van Cauwenberge et al., 2000).

Late phase response

The late phase response occurs 4-6 hours after antigen stimulation. This phase is characterized by prolongation of symptoms of sneezing, rhinorrhoea but most predominantly a sustained nasal congestion which lasts for about 18-24 hours (Min, 2010). The late phase response is predominantly inflammatory in nature and is characterized by inflammatory cellular influx comprising of predominantly T lymphocytes, basophils and eosinophils. A variety of mediators are released by these cells including leukotrienes, kinins, histamine which results in the continuation of the symptoms and the development of the late phase.

The key to the orchestration of the late phase response lies in the production and release of a variety of cytokines and chemokines like IL-4, IL-13 from mast cells (Prussin and Metcalfe, 2006). These cytokines can upregulate the expression of 'adhesion molecules' like vascular cell adhesion molecule 1 (VCAM-1) on the endothelial cells facilitating the infiltration of eosinophils, T lymphocytes and basophils into the nasal mucosa. In addition, chemokines like RANTES, eotaxin, MCP-4 and Thymus and Activation - Regulated Chemokine (TARC) released from epithelial cells serve as chemoattractants for eosinophils, basophils and T lymphocytes (Kay, 2001). Other action of other cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF) released largely by epithelial cells and IL-5 from mast cells prolong the survival of the infiltrated eosinophils in the nasal mucosa leading to persistent symptoms of allergy (Togias, 2000). In addition, a variety of other mediators released like eosinophil cationic protein (ECP), platelet activating factor, major basic protein (MBP) are also implicated in the late phase response.

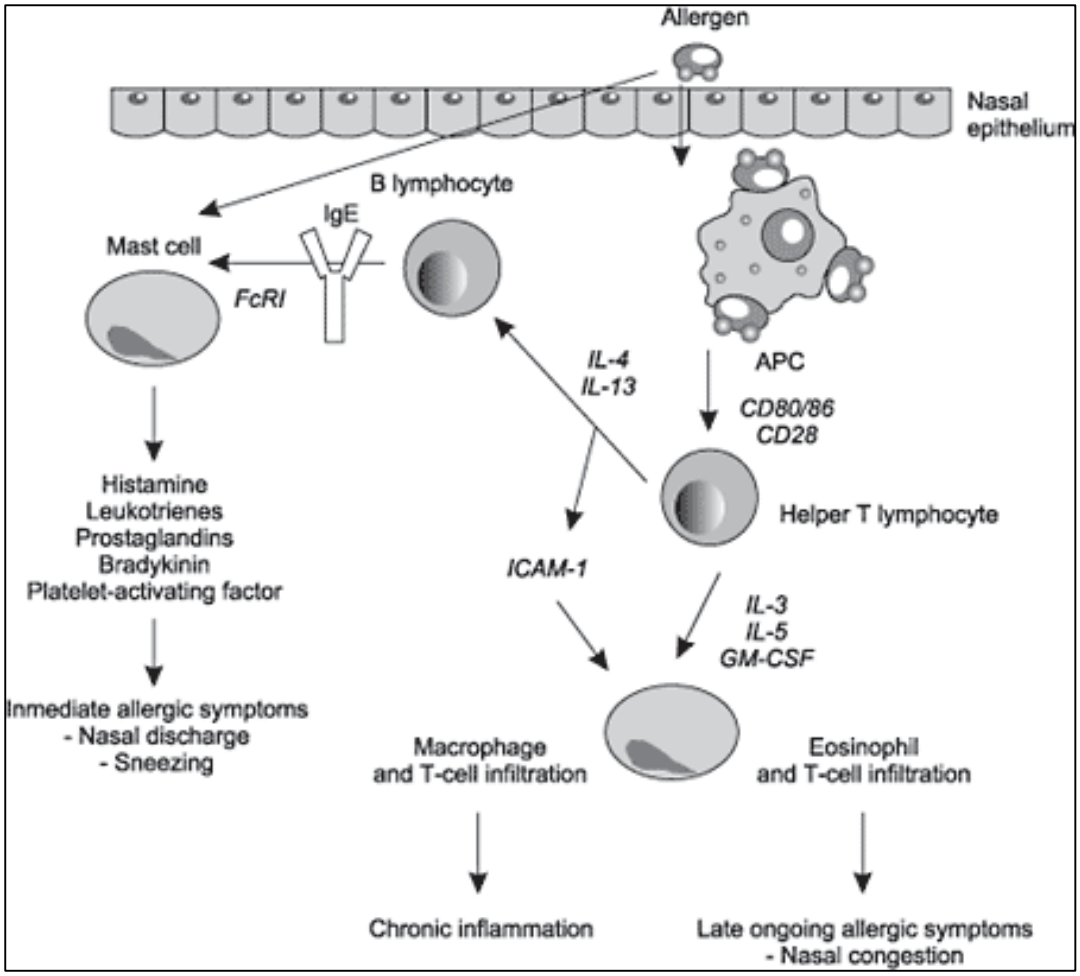

Figure 2. 3- Pathophysiology of Allergic Rhinitis

(Adapted from Drugs Today 2003, 39(6): 451, ISSN 1699-3993, CCC: 1699-3993 DOI: 10.1358/dot.2003.39.6.799450)

2.6 Diagnosis

The diagnosis of IgE-mediated hypersensitivity diseases is routinely based on 4 parameters of evidence. Three types are part of the clinical work-up for allergy which involves a detailed patient history and physical examination, skin testing and in certain condition, challenge testing with suspected allergen. The fourth type involves laboratory procedure which commonly utilizes in vitro determination of circulating serum IgE antibodies specific for allergen (Kranke and Aberer, 2009).

Thorough history taking can be aided using standard questionnaire such as Total Nasal Symptoms Score (TNSS) which can assess the severity of the disease impacts to the patient's quality of life. All relevant past history, other medical co-morbidites, dietary, drugs and allergy history as well as social history such as environmental and occupational exposure needs to be elucidated. Undoubtedly, not to be forgotten to ask the main complaint of the patient which lead to the four cardinal symptoms of allergic rhinitis namely sneezing, rhinorhea, itchiness and nasal blockage.

There are many differential diagnosis of allergic rhinitis and one of them includes non-allergic rhinitis (NAR) which subdivided into 8 major subtypes which includes nonallergic rhinopathy (previously known as vasomotor rhinitis), nonallergic rhinitis with eosinophilia, atrophic rhinitis, senile rhinitis, gustatory rhinitis, drug-induced rhinitis, hormonal-induced rhinitis, and cerebral spinal fluid leak (Tran et al., 2011).

Physical examination should be included to assess general condition of the patient and to look for obvious allergic signs such as allergic shiners which is a dark circles around the eyes and allergic nasal crease or allergic salute which is a horizontal crease across the lower half of the nasal bridge due to repeated upward rubbing of the tip of the nose. A full ear, nose, throat examination is performed emphasizing on the other sign of allergy in ocular, pharynx and larynx. Current approach advocated that nasal endoscopy offers an advantage of global evaluation of the endonasal cavity compare to the anterior or posterior rhinoscopy examination (Scadding et al., 2011). Besides that, the scoring methods also valuable in management of allergic rhinitis during follow up (Table 2.2).

Table 2. 2- Endoscopic Appearance Score

Adapted from; Laryngoscope. 2014 Oct; 124(10):2216-23. doi: 10.1002/lary.24654. Epub 2014 Apr 2 Modification of the Lund-Kennedy system by excluding the subscores of scarring and crusting improves its reliability (Psaltis et al., 2014).

Characteristic	Right nasal cavity	Left nasal cavity
Polys (0,1,2)		
Edema (0,1,2)		
Secretions (0,1,2)		
Total		

Scoring:

	0	1	2
Polyp	Absent	Limited to middle meatus	Extend into the nasal cavity
Mucosal oedema	Absent	Mild/moderate oedema	Polypoid degeneration
Secretion	Absent	Hyaline	Thick and/or mucopurulent

2.6.1 Symptoms and Signs

AR showed immediate-type allergic symptoms of sneezing, rhinorhea, itchiness and nasal obstruction. Manifestation of AR symptoms varies depending on its severity to a patient based on impairing daily activities such as repetitive sneezing, severe rhinorhea causing nasal congestion, loss of smell and postnasal drip, itchy red eyes and excessive tearing, fatigue and malaise. Current approach for the management of AR follows the Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines (Pawankar et al., 2012).

The ARIA classification introduced a systematic approach for assessing severity of AR on the basis of the presence or absence of impairment in any of 4 health-related quality of life(HRQL) items which are sleep, daily activities/sport, work/school and troublesome symptoms. ARIA workshop group defines AR as mild when there was no impairment in any of these items and moderate or severe when there was impairment in one or more areas.

Table 2. 3- Classification of Allergic Rhinitis based on duration

Intermittent symptoms	Persistent symptoms
Less than 4 days per week or	More than 4 days per week
Less than 4 weeks per year	More than 4 weeks per year

Table 2. 4-Summary of ARIA classification (combination of duration and severity)

Mild	Moderate to Severe (one or more items)
Normal sleep	Abnormal sleep
Normal daily activities, sport, leisure	Impairment of daily activities, sport, leisure
Normal work and school	Problem caused at work and school
No troublesome symptom	Troublesome symptom

In certain centres, patient with symptoms of AR, need to undergo nasoendocope examination for evaluation of the whole nasal cavity, septum, nasopharynx and also the area of middle meatus which has clinical importance in rhinosinusitis. However, some centre only performed anterior rhinoscopy for diagnosing AR without any other laboratory testing. According to the Joint Task Force on Practice Parameters by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) advocates that the nasal and oropharyngeal examination may be accomplished with a nasal speculum with appropriate lighting, otoscope with nasal adapter, indirect mirror, and/or rigid or flexible nasopharyngoscope, based on the expertise of the examiner and/or the assessment needs (Wallace et al., 2008).

2.6.2 Skin Prick Test

A skin test for allergic testing is widely used among physicians. There are 2 types of skin test which are epidermal and percutaneous test. Examples of epidermal test are patch test and friction test whereas percutaneous test for example are skin prick test (SPT), scratch test and transdermal test.

Rapid detection of allergen specific IgE is an essential tool in the clinical practice of allergy. Remarkably, the skin prick test is the most widely used diagnostic test in allergy because it is simple, quick and most sensitive method detecting specific IgE. Therefore, in this study also, we used SPT for testing of allergic to the patient.

SPT may provide information regarding type of allergen sensitivity although results of SPT must always be interpreted in combination with history and clinical findings. The potential value of SPT also depends upon the quality of the allergen extracts used and the technical performance of the operator. Extracts should be biologically standardized with low batch-to-batch variation. Solutions should be made up with preservative and generally stored in a refrigerator at +4 degree Celsius. There is variability of shelf life of allergens extract between different manufacturers. In general, SPT are more sensitive than in vitro determinations of allergen-specific IgE. SPT also can be performed to identify allergen before starting allergen-specific immunotherapy. In addition, upon completion of SPT procedure, it serves educational value and provide a visual evidence to reinforce verbal advice to the patient about allergen avoidance measures.

Table 2.5 - Indication of Skin Prick Test (European Standard)

Indication
rhinoconjunctivitis
Asthma
Urticarial
anapylaxis
atopic eczema
food allergy
drug allergy

Table 2. 6 - Relative Contraindication of SPT (European Standard)

Relative contraindication
Pregnancy (in view of a remote possibility of inducing a systemic allergic reaction that could induce uterine contractions or necessitate the use of epinephrine)
severe eczema, dermographism
Individual who is on antihistamines or other medications such as certain anti-depressants or calcineurin inhibitors

The recommended method of skin prick testing includes the appropriate use of specific allergen extracts, positive and negative controls, interpretation of the tests after 15 – 20 minutes of application. A positive result defined as a wheal ≥3 mm diameter (Heinzerling et al., 2013).

Practices points for SPT:

- Always check that patient is not on antihistamines before performing SPT
- Always include positive (histamine) and negative (allergen diluent) control tests
- A positive test is (arbitrarily) 3mm or more greater than the negative control
- SPT should be performed on the flexor aspect of the forearm using a sterile lancet
- The procedure should not be painful and not draw blood
- Dermographism may confound results
- A measurement of allergen-specific IgE concentration (RAST) is an alternative if skin prick test cannot be performed

SPT is considered as the conventional method to test for the presence of allergen-specific IgE and to detect IgE bound to the surface of mast cells in the skin. The principle of SPT is when a solution of allergen is applied to the skin at the volar surface of the forearm. The allergen will have contact with specific IgE bound to the surface of cutaneous mast cells upon skin pricked using lancet. The binding of the allergen leads to cell activation and the immediate release of mediators including histamine. Other mediators are also released but histamine appears to be the critical one as skin prick test becomes negative after taking oral antihistamines. The release of mediators result in a wheal and flare type reaction and the test is generally reported as the maximal wheal diameter after 15 to 20 minutes. The test is reported as positive if the diameter size of a wheal is 3mm or more than the control.

These tests are simple, quick and the most sensitive method of detecting specific IgE. SPT are particularly helpful in excluding potential allergens as a cause of symptoms as false negatives are common. Although this test are extremely safe with only rare reports of generalized reaction, the risk of systemic absorption remains and anaphylaxis is a remote possibility in highly sensitized individuals. Testing should be performed by experienced personal and resuscitation equipment should always be available.

2.6.3 Inflammatory markers

Blood inflammatory marker is another option for patient when SPT is contraindicated. Such patients are those at high risk anaphylaxis, small children, severe dermatographism or severe eczematous dermatitis. There are few types of inflammatory markers that can be used as allergy markers in the human serum.