2. REVIEW OF LITERATURE

2.1 Epidemiology of Asthma in India

Pulmonary diseases which include bronchial asthma and Chronic obstructive pulmonary disease which are chronic in nature and causes 7% of deaths and 3% of loss of Disability Adjusted Life Years (DALYs). The previously published studies reported highly variable prevalence’s of both asthma and COPD. Many reason for the differences is in their definitions of diseases, methodologies, analysis and interpretation. A multi-centre population study, Indian study on Epidemiology of Asthma, Respiratory symptoms and Chronic bronchitis (INSEARCH) was therefore undertaken in two phases- 4 centres in phase I and 12 centres in phase II. The centres, both rural and urban, were spread over different parts of India. The study employed uniform definitions and methodology (Jindal, 2012).

A two stage stratified sampling design was used considering the district as a unit. The study- questionnaire was based on the Union’s English questionnaire (1984), translated to Hindi and other regional languages, tested for its reliability and validity. The questionnaire-diagnoses of asthma and chronic bronchitis (CB) were based on separate sets of questions which were pre-defined before the analyses. The national burden was calculated based on the standardized prevalence estimates as per the 2011 population estimates.

The Phase I study included 73605 individuals of whom 2.38% were diagnosed to have asthma. Chronic Bronchitis (CB) was diagnosed in 4.1% of 35295 subjects of over 35 years of age. The study population consisted of 85103 men and 84470 women in the Phase II study. The overall prevalence of asthma and CB were 2.05% (adults aged ≥ 15 years age) and 3.49% (adults of ≥ 35 years of age) respectively.

Smoking, asthma in first degree relatives, unclean cooking fuels, advanced age household environmental tobacco smoke exposures were associated with increased odds of asthma and CB. The national burden of asthma and CB was estimated at 17.23 and 14.84 million respectively.

The INSEARCH report provides good estimates of the population prevalence’s, risk factors and national burden of asthma and CB in India.
Table 2.1
Prevalence of Bronchial Asthma in various cities in India

<table>
<thead>
<tr>
<th>S.No</th>
<th>City</th>
<th>Prevalence of BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Delhi</td>
<td>1.69</td>
</tr>
<tr>
<td>2</td>
<td>Chandigarh</td>
<td>2.28</td>
</tr>
<tr>
<td>3</td>
<td>Kanpur</td>
<td>2.05</td>
</tr>
<tr>
<td>4</td>
<td>Kolkata</td>
<td>4.82</td>
</tr>
<tr>
<td>5</td>
<td>Mumbai</td>
<td>0.87</td>
</tr>
<tr>
<td>6</td>
<td>Bangalore</td>
<td>3.47</td>
</tr>
<tr>
<td>7</td>
<td>Chennai</td>
<td>1.27</td>
</tr>
<tr>
<td>8</td>
<td>Trivandrum</td>
<td>3.44</td>
</tr>
<tr>
<td>9</td>
<td>Ahmedabad</td>
<td>1.90</td>
</tr>
</tbody>
</table>

Legend: BA – Bronchial Asthma

2.2 Food allergens

Food is an important factor in causing allergic diseases like asthma, urticaria, rhinitis etc., The occurrence rate of food allergy was 6 to 8% in infants and 1.5% in adults (Lessof et al., 1980) were allergic to food. When compared to adults, children are reported to be more sensitive to foods and ingestion of highly allergic food had caused death in children, adolescents and adults (Yunginger et al., 1992). The main food allergens are peanuts and nuts. They are more sensitive to minute quantities of food allergens (Blancocarmona et al., 1992) and even to inhalation of food allergens present in air or in cooking fumes (Valero Santiago et al., 1988). Even chemical substances like sulphates, sulphites, processing of fish, dried fruits, vegetables, potatoes, wine, beer, bottled lemon or lime juice, pickled foods have been found to trigger asthma (Smith, 1990).

Allergic reactions to food can be divided into toxic reaction and non-toxic reaction. Adverse reactions to food can be divided into non-immune mediated and immune mediated. They are called food allergic reactions. Food allergy is an IgE mediated type I hyper sensitivity reaction which leads to symptoms within hours of having ingested the food causing lip, tongue and throat burning or itching, nausea, abdominal cramps, diarrhoea and erythema (Dixin, 2000). Sometimes it can cause
asthma, shortness of breath, fast heart rate, panic and confusion and rarely causes anaphylactic reaction. Asthma appears to be an important risk factor for this type of allergy (Oppenheimer et al., 1992). It has been estimated that less than 10% of asthmatics may have noticed that their symptoms are provoked by certain foods or drinks (Onorato et al., 1986). 37% of children with atopic dermatitis have food allergy. Food sensitivity is a delayed immune response which is mainly IgG mediated, that includes chronic symptoms like gut pain, diarrhoea, constipation or anxiety. Because the reactions are very subtle and delayed for hours or day or more, IgG mediated food allergies are very difficult to recognize.

In United States in children under 2 years of age, the common food allergens were egg, milk, peanut, soya beans and wheat (Marshall plaut, 1997). In Spain, egg albumin, cow’s milk, and peanuts were common food allergens in children in the age group of 2 years. After 4 years, vegetable allergens such as nuts, fruits and legumes were the most frequent allergens (Pascual, 2000). In Swiss children (Eiggnmann, 2000), the foods most frequently incriminated were egg, milk and peanuts. All food allergens commonly affected the children under the age of six years (Sampsyn and Mccaskill, 1985).

According to Bhattacharya (2013) in India the most important food allergens were milk, eggs, fish, peanuts, soya bean, yeast, cheese, wheat, rice and chocolates which may be causing the asthma. The main food allergens in and around Pollachi were peanut and potato in 2 to 5 years age group and potato and crab in 6 to 10 years age group.

From this, it was evident that food allergens varied in children in Western countries when compared to our children of that age group. In this study cow’s milk, egg yolk, milk powder and chicken were not important food allergens as in the case of children in Western countries. Out of 35 children in the age group of 2 years to 10 years, only one child was allergic to cow’s milk, one child to egg yolk.

Incidentally it was noticed that persons who did not eat crab, fish and prawn were allergic to crab and shrimp/prawn. The specificity of IgE tests with foods was affected by the existence of homologous food allergens which induced cross-reactive IgE. Various clinical cross-reactivity was noticed among botanically-related fruits, different nuts, mammalian foods and sea foods than cereals, grains and legumes (Kochuyt, 2006). Shrimp antigen II, Metcalf et al., 1991 which was heat stable, and a variety of other antigens were shared by several crustaceans, including shrimp, prawns, crabs, lobsters.
and crayfish. It may be the reason why patients who had not eaten crabs and prawns were allergic to these foods substances.

Rao et al., in their study on prevalence of food allergen in Bangalore with 118 persons reported that the main food allergens were crab, potato and peanut. It was in line with this study. But other few prevalent allergens in their study were coffee (60 persons), chicken (58 persons), apple (57 persons) and grape (52 persons), which differed markedly with the result of this study.

Hence the sound knowledge of ‘food allergens’ prevalent in that area is essential to diagnose and treat food allergy and atopic diseases.

2.3 Histamine-synthesis, action and metabolism

It is essential to know the synthesis, mode of and site of action of histamine, its effects upon various organs of our body and how it is metabolized and eliminated from the blood circulation.

Histamine \([2 – (4 – \text{Imidazolyl}) \text{ethylamine}]\) is a widely distributed substance in peripheral tissues, where it mediates a variety of physiological activities including inflammation, gastric acid secretion and smooth muscle co-contraction. Histamine was discovered in 1910 by Dale and Laidlaw.

Histamine is localized in mast cells, neuronal cells, neuroendocrine cells of the gastric tract, lung and kidney, in cerebrovascular endothelial cells and throughout the peripheral nervous system. Histamine is formed by decarboxylation of its precursor, L-histidine, by the enzyme L-histidine decarboxylase. It belongs to the biogenic amines.

Histamine is synthesized by mast cells, basophils, platelets, histaminergic neurons, and enterochromaffine cells, where it is stored intra-cellularly in vesicles and it is released on stimulation. Besides the allergens cross-linking the FcεRI receptors or mast cells causing triggering of degranulation, several other non-immunologic stimuli, such as neuropeptides, complement factors such as C3a and C5a, cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases, hypoxia, chemical and physical factors (e.g., traumas, extreme temperatures) or alcohol and certain food and drugs, may activate mast cells.
2.3.1 Action of Histamine

Histamine exerts its effects by binding to its 4 receptors (H₁R, H₂R, H₃R and H₄R) on target cells in various tissues (Raithel, 1999).

It causes smooth muscle contraction. Vasodilation – increased vascular permeability. Viscid mucus secretion. Arrhythmias and alterations of blood pressure. It stimulates gastric acid secretion and nociceptive nerve fibres.

Histamine plays a role in neurotransmission, immunomodulation, haematopoiesis, wound – healing, day – night (circadian) rhythm, regulation of histamine and polyamine – induced cell proliferation and angiogenesis in tumor models and intestinal ischaemia.

2.3.2 Metabolism

Histamine is metabolized in two ways.

- By Oxidative deamination by DAO
- By ring methylation by histamine – N – methyltransferase (HNMT) (Schwelberger, 2004).

The DAO (oxidative deamination) protein is stored in plasma membrane – associated vesicular structures in epithelial cells and is secreted into the circulation on stimulation. Therefore it has been proposed that DAO maybe responsible for scavenging extracellular histamine (e.g., after ingestion of histamine - rich food), after mediator release.

DAO expression is restricted to specific tissues, the highest activities seen in small bowel and ascending colon, placenta, kidney, etc., (Raithel, 1999)

Conversely, HNMT (histamine – N – methyltransferase) the second most important enzyme inactivating histamine, is a cytosolic protein, which can convert histamine only in the intracellular space of cells. HNMT is widely expressed in human tissues like kidney and liver, followed by spleen colon prostate, ovary, spinal cord cells, bronchi and trachea. HNMT is regarded as the key enzyme for histamine degradation in bronchial epithelium.

2.3.3 Causes of Histamine intolerance

The histamine intolerance may be due to increased availability of histamine or due to impaired histamine degradation.
2.3.3.1 Conditions for Increased availability

Endogenous histamine over production caused by allergies, mastocytosis, bacteria, gastro-intestinal bleeding, or increased exogenous ingestion of histidine or histamine by food or alcohol. Other biogenic amines such as putrescine, may also be involved in displacing histamine from its mucosal mucine linkage, which results in an increase of free absorbable histamine in circulation.

2.3.3.2 Impaired histamine degradation

May be due to genetic or acquired impairment of the enzymatic function of DAO or HNMT. DAO inhibits the trans-epithelial permeation of exogenous histamine and impaired DAO activity results in increased enteral histamine uptake with consequent increased plasma histamine concentrations and corresponding symptoms (Sattlar, J., Lorenz, W., 1990).

2.3.4 Clinical picture

The normal basal plasma concentration of histamine is 0.3 to 1.0 ng/ml. Exceeding the individual histamine tolerance gives rise to histamine mediated symptoms which are concentration dependent.

<table>
<thead>
<tr>
<th>Histamine (ng/ml)</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Reference</td>
</tr>
<tr>
<td>1-2</td>
<td>Gastric acid secretion, heart rate↑</td>
</tr>
<tr>
<td>3-5</td>
<td>Tachycardia, headache, flush, urticaria</td>
</tr>
<tr>
<td>6-8</td>
<td>Arterial pressure↓</td>
</tr>
<tr>
<td>7-12</td>
<td>Broncho-spasm</td>
</tr>
</tbody>
</table>

Inhibition of DAO followed by oral histamine administration may induce severe and even life threatening reactions such as hypotension, bronchospasm or shock. In patients with hyper histaminemia, recurrent anaphylactic reactions have been reported (Table 2.2).
Typical symptoms of histamine intolerance include gastrointestinal disorders, sneezing rhinorrhoea and congestion of the nose, headache, dysmenorrhoea, hypotonia, arrhythmias, urticaria, flushing and asthma.

Symptoms can be manifest via the above mentioned actions of histamine in multiple organs such as the gastrointestinal, lung, skin, cardiovascular system and brain, according to the expression of histamine receptors.

2.4 Studies on asthma and allergic rhinitis, among occupational hazardous workers in and around Pollachi

Analysis of results obtained from spinning mill and coir industry workers showed a prevalence rate of 12.7% and 15.5% respectively. When compared to the occurrence rate of bronchial asthma in rural and urban area it was 10 to 12%. The prevalence rate of B.A. was more or less same, i.e. 10 to 15% in all three types of areas – industrial, urban and rural. From the above study, it was concluded that the

1) occurrence rate among industrial workers who were exposed to dust constantly at the working place was as that of people living in urban and rural area.

2) the allergens like dust and husk were not causative factors for Bronchial asthma (Manohar et al., 2017).

2.5 Allergic Rhinitis and co-morbid Asthma: Perspective from India –Pacific Workshop Report

In India, allergic rhinitis (AR) is considered to be a trivial disease, despite the fact that symptoms of rhinitis were present in 75% of children and 80% of asthmatic adults. House dust mite (Dermatophagoides farinae) was the most common allergen. Studies conducted in India have shown that AR often restricts the patient’s quality of life (QOL). It can affect the physical, psychological and social aspects of the patient’s life and can also impact their functions at work. Furthermore, AR adversely affects sleep related QOL. In spite of causing a major impact on the QOL in Indian patients, AR is rarely given the importance it deserves (Ashok and Ruby, 2009)
2.6 Environmental risk factors for respiratory and skin atopy: Results from epidemiological studies in former East and West Germany

From the year 1990 onwards, comparative epidemiological studies were performed between various regions in former East and West Germany with yearly questionnaires and 3 years physical, dermatological, allergological and exposure examination in a total of about 30,000 preschool children. There were striking differences between the various German regions with higher prevalence rates of respiratory atopy (hay fever, asthma) and atopic sensitisation (prick test, RAST) in West Germany, while atopic eczema was significantly higher in East Germany. Total serum IgE levels were markedly higher in children in the east of Germany, similar to the prevalence of parasite infestation (Ring et al., 1999).

2.7 Asthma Epidemiology in Chinese: What have we learnt so far?

Assessed using ISAAC study phase I, II & III. Standard written and Video Questionnaire – Chinese children from Hong Kong were found to have the highest prevalence rate of wheeze than children from mainland China and it was 12.4% and 10.1% respectively; in children from mainland China, they were 4.2% and 2% respectively. It is suggested by the author that early environmental and social exposure factors most likely can influence the subsequent development of asthma.

In phase III ISAAC study in 2002 using the same standardized and validated protocol, the data were compared with Phase I, study (1995) data. The prevalence rates did not change significantly. They were 11.2% and 10.2% respectively. It appears that the prevalence of asthma has not increased over the last 7 years and the control of asthma appeared to have improved.

In phase II ISAAC study from 3 Chinese cities – Hon Kong, Beijing and Guangzhou in 10000 children to determine the possible risk factors that are associated with the development of asthma – Attendance of day care and the presence of siblings was also found to be associated with reduced risk of asthma symptoms – in line with what is suggested by the ‘hygiene hypothesis’ – frequent early infections may induce Th-1 predominance resulting in relative resistance to the development of atopic disorders (Wong, 2005).
Over the past decade, many research studies have confirmed the protective role of traditional role of type of living such as living in a farming environment as suggested by the ‘hygiene hypothesis. It should be emphasized that there is no proven primary preventive strategy for asthma.

2.8 Asthma and Rhinitis in cleaning workers; a systemic review of epidemiological studies

This article presents a systematic review of epidemiological studies linking cleaning work and risk of asthma and rhinitis. They collected and reviewed 24 papers from PubMed, covering the years from 1976 through June 30, 2012. Increased risk of asthma or rhinitis has been shown in 79% of included epidemiological studies.

The increased risk of asthma in cleaning workers was confirmed by objective tests such as bronchial hyper reactivity or air flow obstructions. Level of exposure to cleaning products, cleaning sprays, bleach, ammonia, mixing products and specific job tasks has been identified as specific causes of asthma and rhinitis. It is concluded that possible prevalence measures encompass the substitutions of cleaning sprays, bleach and ammonia, avoidance of mixing products, the use of respiratory protective devices, workers education and medical surveillance (Siracusa, 2014).

2.9 Familial aggregation and heritability of asthma associated quantitative traits in a population based sample of unclear families.

Although asthma is a common disease, genetically it is a complex human disease. The familial syndrome of atopy (allergic asthma, seasonal rhinitis and/or eczema) is accompanied by increased levels of total serum Immunoglobulin E (IgE) and elevated levels of IgE specific to common aero allergens. In patients with asthma specific serum IgE is most commonly detected against inhaled allergens from house dust mites (HDM) and grass pollens. Variably reduced spirometric measures such as the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) are closely but not specifically associated in the asthma and atopy. Asthma is also characterized by elevated blood eosinophil counts and by non-specific increased airway responsiveness (AR) to inhaled agonists such as histamine or methacholine, which can be quantified by measuring the reduction of expiratory airglow following increasing doses of these
agents. Our study suggests that total and specific serum IgE levels, blood eosinophil counts and airways responsiveness to inhaled agonists are appropriate phenotypes for molecular investigations of the generic susceptibility to asthma. Whole genome screens investigating linkage of asthma and associated phenotypes are consistent with the results of this study; significant linkage to serum IgE levels, blood eosinophil counts and/or AR has been found in the majority of genome screens. The specific genes responsible for the heritabilities of serum IgE levels, blood eosinophil counts, FVC and AR remain to be defined as do their inter relationships with environmental factors (Palmer et al., 2000).

2.10 Different Profiles of IL – 10 + IFN-γ- il – 4 – CD4+ T cells in the Peripheral Blood in Atopic and Non Atopic Asthmatics

The impaired production of interleukins (IL) 10 from regulatory T cells has been proposed as a causal mechanism of asthma. Although IL - 10 producing (IL – 10 +) T cells are detectable in the peripheral blood, their significance in the pathophysiology of asthma remains uncertain. The peripheral blood mononuclear cells (PBMCs) of atopic and non-atopic asthmatics were stimulated with anti – CD 3 and anti CD 28 antibodies and then processed for triple cytokine flow cytometry directed to IL – 10, interferon (IFN) γ AND IL – 4. The results showed that IL – 10 + CD 4 + cells in PBMCs may be distinct from Th1 or Th2 and likely have the profile of regulatory T cells. The differential association of IL – 10 + IFN – γ – IL4 – CD4 + cells with clinical severity pathophysiological significance may differ among asthma phenotypes (Matsumoto, 2008).

A unique population of T cells showing a regulatory role onto a variety of Th1 – and Th2 type immune response was identified during the last decade. A part of the population plays its regulatory role through the selective production of IL–10. IL–10 is known to inhibit the expression of the MHC class II molecule and co-stimulatory molecules on antigen – presenting cells. In addition, experimental asthma models have shown that defective IL – 10 results in the exacerbation of airway inflammation. In conclusion, IL–10 + CD4 + cells with PBMCs of asthmatics selectively produce IL–10, but not IL–4 or IFN-γ, which is suggestive of the people of regulatory T Cells.
2.11 Therapeutic effects of histobulin – with special reference to bronchial asthma and others

The patients with allergic diseases, especially with a focus on bronchial asthma, allergic rhinitis and atopic dermatitis were treated with HISTOBULIN. The subjects population of the present study were 52 out, and in patients in our Allergic section; 2nd Dept. of Internal Medicine, the breakdown of whom were 35 cases of bronchial asthma (23 males and 12 females), 8 cases of atopic dermatitis (3 males and 5 females) and 9 cases of allergic rhinitis (5 males and 4 females), the age ranged from 5 to 77 years, in an average of 33.9 years (Fukuda, 1974).

2.11.1 Administration method and efficacy judgment

- One vial of Histobulin, as a rule, was subcutaneously injected once weekly-10 dose regimen was applied as one course of Histobulin treatment and further, a booster dose was injected once per 2 to 4 weeks.

- The criteria for efficacy evaluation were: the cases achieving elimination of subjective symptoms were judged as ‘improved’; alleviation of subjective symptoms as ‘slightly improved’ and no change or aggravation in said symptoms as ‘not improved’.

The therapeutic efficacy of Histobulin was recognized in 86.5% of the treated patients when summing improved and slightly improved cases, the breakdown for each specific diagnosis were, out of 35 patients of bronchial asthma,18 improved, 12 slightly improved and 5 not-improved cases were recorded-indicating a response rate of 85.7%, out of 8 atopic dermatitis, 5 improved, 2 slightly improved and 1 not-improved cases marked a response rate of 87.5%, in 9 cases of allergic rhinitis- response of 88.9% was given by 6 improved, 2 slightly improved and 1 not-improved cases. The development of Histobulin might be declared to have realized the broad use from aged to infantile patients and to have established the high therapeutic efficacy regardless of the type of bronchial asthma (Tohru yamamoto et al., 1974).
2.12 Gamma globulin – Histamine complex in the treatment allergic disorder of respiratory tract:

Gamma globulin- histamine combination was used in our chest clinic in allergic disorders of the respiratory tract. The Product: Gammalergen (Histaglobin) contains Human normal immunoglobulin 12mgs; Histamine Dihydrochloride 0.15 µg and Sodium Thiosulphate 32 mgs as lyophilized powder to be dissolved in 2 ml solvent water for injection.

This complex of gamma globulin-histamine (Ashokan Suhumaran, 1982), confers upon the allergic individual a true antihistamine immunity. It certainly modifies the allergic field. Studied the effects of drug in 42 patients

Dose schedule

a)1 vial subcutaneously once a week x3 doses.
b)1 vial subcutaneously once a month x3 doses.
c)1 vial subcutaneously once in 3 months to complete 2 years.

A total of 12 doses on an average was given during a period of 24 months. The cases who followed up for one more year.

Gamma globulin- Histamine complex is a good weapon in the armamentarium in the treatment of allergic disorders of respiratory tract by virtue of its scientific basis, low cost, and remains appealing due to its technical simplicity.

2.13 Evaluation of histamine – gamma globulin (Histaglobin) in the treatment of various allergic conditions

Histaglobin was studied in the allergy clinic of Gouverneur Hospital, New York city in 54 patients. Histaglobin was administrated by subcutaneous injection in doses of 2cc once a week for 3 weeks. Results showed that a significant number of patients experienced a symptoms free period which lasted from at least two to seven months. In case of seasonal hay fever, the results were least satisfactory, but very gratifying in all of the others conditions treated.
It appears that Histaglobin in some way, as yet unexplained, profoundly alters the allergic state in a significant proportion of patients suffering from intermittent attacks of the sensitization type of bronchial asthma, allergic rhinitis, atopic dermatitis and urticaria and that a more extensive investigation is justified (Harold Gelfand).
3. OBJECTIVE

To estimate and compare the Serum Histamine Binding Capacity in normal and allergic persons and to establish that serum histamine binding capacity (SHBC) is more in normal persons than in allergic patients.

1. To estimate total Immunoglobulin E (IgE) level in the serum – to find out normal and allergic persons
2. To Separate Antihistamine antibody from the serum.
3. To Analyse the elutes to establish that the elute contains only antihistamine antibody.
4. To know the type of antibody – whether it is IgG or IgM or IgA etc., by bio physical characterisation.
5. To estimate the protein concentration (anti histamine anti body) in the serum.
6. Estimation of Serum Histamine Binding Capacity of allergic and normal sera and to compare the serum histamine binding capacity.