"PREVALENCE OF IRREVERSIBLE AIRFLOW OBSTRUCTION AMONG CHRONIC ASTHMATICS IN GOVERNMENT ROYAPETTAH HOSPITAL"

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BONAFIDE CERTIFICATE

This is to certify that dissertation named "**PREVALENCE OF IRREVERSIBLE AIRFLOW OBSTRUCTION AMONG CHRONIC ASTHMATICS IN GOVERNMENT ROYAPETTAH HOSPITAL"** is a bonafide work performed by Dr. K.Venkatraman, post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfillment of regulations of the Tamilnadu Dr.M.G.R. Medical University for the award of M.D. Degree branch I (general branch) during the academic period from May 2011 to April 2014.

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DECLARATION

I solemnly declare that the dissertation "**PREVALENCE OF IRREVERSIBLE AIRFLOW OBSTRUCTION AMONG CHRONIC ASTHMATICS IN GOVERNMENT ROYAPETTAH HOSPITAL**" was prepared by me at Government Royapettah Hospital , Chennai , under the guidance and supervision of **Prof Dr.N.Gunasekaran M.D, DTCD**, Director and Superintendent , Government Royapettah Hospital, Professor and HOD, Department of Internal Medicine, Kilpauk Medical College, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr.M.G.R Medical University, Chennai** in partial fulfilment of the university regulations for the award of the degree of **M.D Branch I (General Medicine)**.

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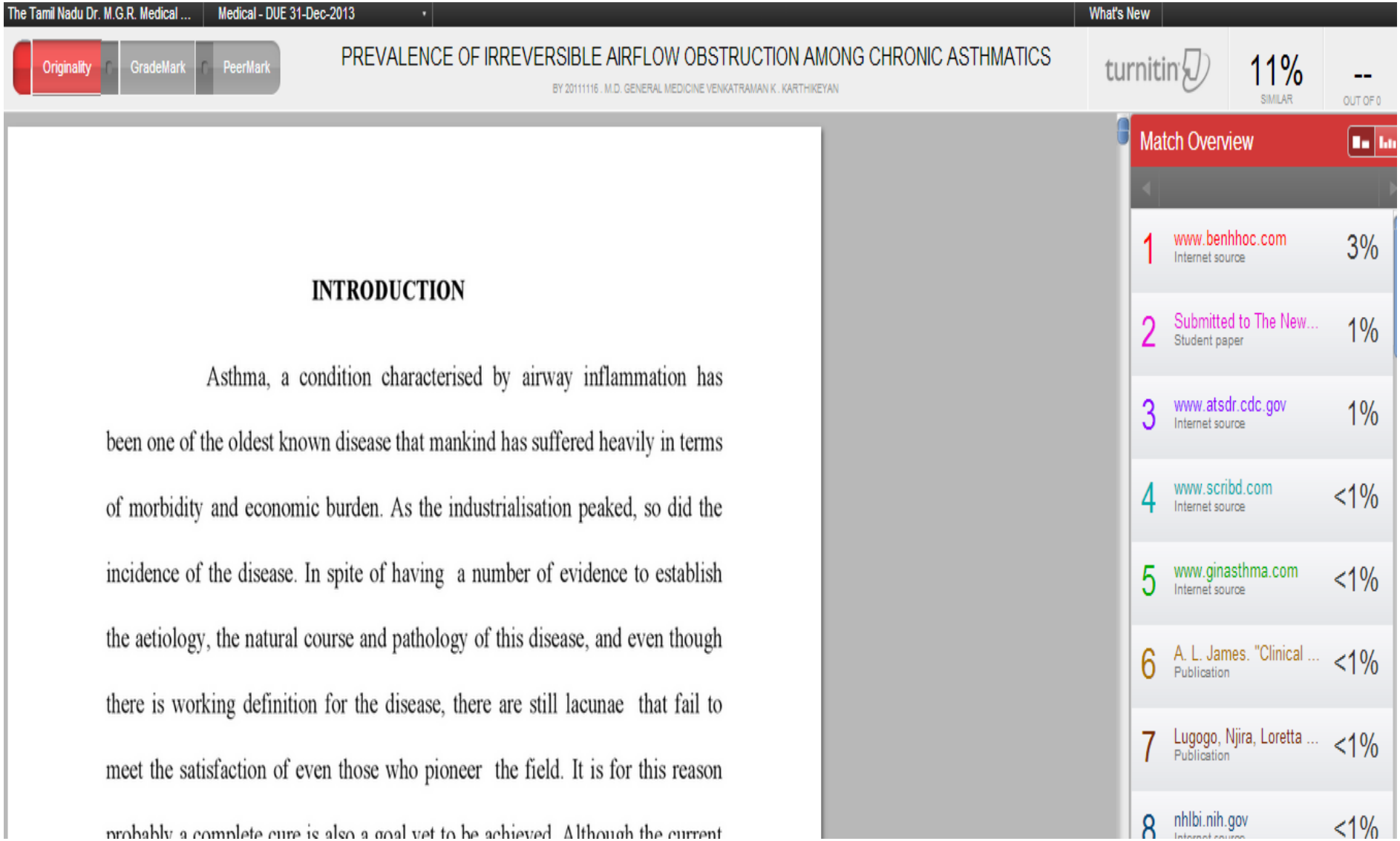
CONTENTS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Asthma, a condition characterised by airway inflammation has been one of the oldest known disease that mankind has suffered heavily in terms of morbidity and economic burden. As the industrialisation peaked, so did the incidence of the disease. In spite of having a number of evidence to establish the aetiology, the natural course and pathology of this disease, and even though there is working definition for the disease, there are still lacunae that fail to meet the satisfaction of even those who pioneer the field. It is for this reason probably a complete cure is also a goal yet to be achieved. Although the current
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PREVALENCE OF IRREVERSIBLE AIRFLOW OBSTRUCTION AMONG CHRONIC ASTHMATICS IN GOVERNMENT ROYAPETTAH HOSPITAL

BACKGROUND:

Asthma is a chronic inflammatory airway disorder characterized by airway hyper responsiveness and reversible airflow obstruction. Subgroups of asthma patients develop airflow obstruction that is irreversible or only partially reversible and experience an accelerated rate of lung function decline. Airway remodelling has been associated with increased disease severity. Irreversible and partially reversible air flow obstruction(COPD pattern) in asthmatics have been associated with longer duration, reduced pulmonary function early in life, frequent exacerbations, smoking, continuing exposure to a sensitizing agent, and adult-onset asthma and lack of use of inhaled corticosteroids early in the course of the disease.The need to identify this pattern using pulmonary function test is always overlooked. This study looks at those patients with long duration asthma with a irreversible and a partially reversible airflow obstruction and analyses the risk factors that potentiate this phenotype in asthma patients and thereby gives clues towards prevention of lung function decline in asthmatics.

OBJECTIVE:

The objectives of this study are to determine the prevalence of irreversible air flow obstruction in chronic asthmatics using spirometry and to assess the risk factors contributing to the development of irreversible airflow obstruction in chronic asthmatics.

MATERIALS AND METHODS:

Patients who were aged more than 18years with asthma duration >10 years were included. The patients had their defined clinically by Diurnal variation of symptoms, predominantly nocturnal symptoms ,seasonal aggravation of symptoms,presence of nasal polyps,Allergic tendencies to known allergens,positive family history, complete relief of the symptom in the past/present with nebulisation. Patients were thoroughly instructed on the use of spirometer and with the informed consent a FEV1, FVC and FEV1/FVC values were obtained using spirometer before and after salbutamol nebulisation. Steroid trail (40mg for 2 weeks) and the values were assessed after 2 weeks. Irreversible airflow obstruction was defined as a failure to increase the FEV1 by >12% or 200ml. The correlation of various factors like smoking, lack of steroid, duration of asthma and age at onset of asthma with the reversibility of airflow obstruction was assessed in the study group.

RESULTS:

Irreversible airflow obstruction was prevalent (50%)in the study population. Smoking, duration of asthma, severity of asthma were significantly associated with irreversible airflow obstruction ($p<.05$). lack of steroid use and age at onset of asthma had statistically insignificant association($p>.05$).

CONCLUSION:

Although airflow obstruction in asthma is reversible, longer duration of asthma, smoking, severe type of asthma was found to be related to irreversible pattern of obstruction in asthmatics. Also asthma when irreversible mimicked clinically as COPD. Thus this study favours asthma as a predisposing/risk factor for COPD. The study also emphasis the importance of using spirometry in diagnosing and monitoring asthma. The recognition of this pattern among asthmatics help in planning the treatment as in outpatient visits and in Emergency rooms

KEY WORDS: Asthma, irreversible airflow obstruction, spirometry ,FEV1, FVC.

INTRODUCTION

INTRODUCTION

Asthma, a condition characterised by airway inflammation has been one of the oldest known disease that mankind has suffered heavily in terms of morbidity and economic burden. As the industrialisation peaked, so did the incidence of the disease. In spite of having a number of evidence to establish the aetiology, the natural course and pathology of this disease, and even though there is working definition for the disease, there are still lacunae that fail to meet the satisfaction of even those who pioneer the field. It is for this reason probably a complete cure is also a goal yet to be achieved. Although the current definition, sees asthma as a completely reversible airflow limitation a considerable set of population land up with irreversible airflow limitation in their course of life. It is with this background this study has been taken, to identify the set of population with irreversible airflow limitation and the factors that operate to make this condition an irreversible one.

HISTORIC PRELUDE:

The term Asthma was obtained from the Greek word "**aazein"** which means to pant and to breath with open mouth or sharp breath. Descriptions about the disease date back to an era before Christ, the earliest by Hippocrates. The Greek physician Galen(2^{nd} century) in his publishing has described about the disease[1]. Moses Maimonides (12^{th} century), an Egyptian physician, wrote in his book *Treatise of Asthma* that his observations of the symptoms in

asthmatics were seasonal and it mostly started in the cold months as common cold and progressively increased in severity which makes the patient hungry for air and cough until he cleared his chest of sputum. The warm months were relatively free of symptoms. Other suggestions proposed by him were to restrict heavy medications, and sexual activity. Sleep, fluids and chicken soup were encouraged. Jean Baptiste Van Helmont (16^{th} century), a Belgian chemist, also a renowned physician of his period was the first to propose that asthma originated in the lung pipes. The Egyptians practised inhalational therapy by heating herbs over the bricks and inhaling the fumes from it. Chinese practised certain native herbs which had ephedrine as an ingredient in them thus facilitating the beta agonistic action. Bernardino Ramazzini (17^{th} century) was the first to describe the exercise- induced asthma. He also described the association between asthma and organic dust. Asthma was dealt as a psychosomatic disease till the early decades of 20^{th} century. Only after 1960 was the inflammatory pathology of the disease recognised and anti-inflammatory medications were started.

EPIDEMIOLOGY:

GLOBAL BURDEN:

235 million people across the world have Asthma. The prevalence of asthma is estimated to increase by 50% globally every decade [2]. An estimated

increase of 100 million asthmatics is expected around 2025 owing to the expected rise in urban population from 45%-60% [2].

The maximum prevalence rates of asthma population are found in Great Britain and New Zealand. The prevalence rates in both these countries approaching 15-20% respectively [2]. Asthmatic prevalence rate has increased two times the previous rates in the last ten years in Western Europe [4]. Japan has seen a threefold rise in the asthma population over the last decade [2].

With the increasing urbanisation and westernisation trends in the developing countries like Africa, Central and South America, Asia, and the Pacific [2], the incidence of asthma has also started to increase. Prevalence rates are high in South American countries like Brazil, Costa Rica and Peru. In these regions the rates are in the range of 10-15% [2]. Asian countries such as China and India have reported lower prevalence rates (5-10%) [3] when compared to the European countries. But these two countries increase the global burden in terms of number of patients (absolute) [5].

According to the WHO report around two hundred and fifty thousand people died in the year 2004-2005 due to asthma.

An estimated disability-adjusted life year (DALYs) is around 15 million per year due to asthma [6]. The costs of treating Asthma are higher than the cost for treating chronic infections like tuberculosis and HIV/AIDS added together

[7]. Western countries suffer a loss from $300 to $1,300 per patient in a year for treating asthma [8].

Cost of treating asthma was found to be higher in the moderate and severe asthmatics than the mild asthmatics [9].Improper control of asthma has been found to be the detrimental element in raising the cost of treating asthma [10]. Western countries have a strict agenda for the control of the disease and have the majority of their asthma population (70%) in the mild category and thus have their cost cut down in managing the severe group. Treating Asthma exacerbations have been found to be three and half times more costly than treating someone without exacerbations [11].

ASTHMA BURDEN IN INDIA:

The epidemiological data on asthma are low in India. It is presumed that India has low prevalence rate of Asthma rates, although recent numbers shows that the actual prevalence is higher than what was initially thought [5].The prevalence of asthma in the total population is 3%(30 million) and the adult population (over 15 yrs) contributed 2.4% of the total population.

The National Family Health Survey (NFHS)-3 conducted a cross sectional study to find out the prevalence rates of asthma in India. The gender wise distribution of asthma was almost similar amounting to 1,696 and 1,627 per 100,000 respectively [12]. The prevalence rate increased with age. Prevalence of asthma is higher in rural areas than urban areas. It is also less common in

men than women. Male asthmatics are more clustered in the lower economic sections than the higher economic sections. Prevalence rates topped among people with <five years of schooling (2,283 /100,000 in women and 2,640/100,000 in men). People with no education had a relatively lesser prevalence (1,914/ 100,000 in women and 2,440/ 100,000 in men)[12].

Amongst the individual states the North east regions of India were found to have high prevalence rates. The prevalence among women was found to be the lowest in Himachal Pradesh (384/100000) population and highest in Tripura (5924/100000). Women asthmatics over 1000/100000 population were seen in 23 states and 5 states showed more than 3000/100000 population. The states were: West Bengal, Kerala, Mizoram, Tripura and Sikkim. Amongst men Jharkhand had the lowest prevalence (407/100000) and Tripura the highest (5086/100000). Only two states namely West Bengal and Tripura had a male asthmatic population of over 3000/100000.

REVIEW OF LITERATURE

DEFINITION OF ASTHMA:

The definition of asthma as per the global initiative of asthma [13] is as follows

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

RISK FACTORS:

There are numerous risk factors associated with development of asthma. They may be isolated or may overlap in bringing out the phenotype of the disease. The risk factors known to be associated with asthma are as follows.

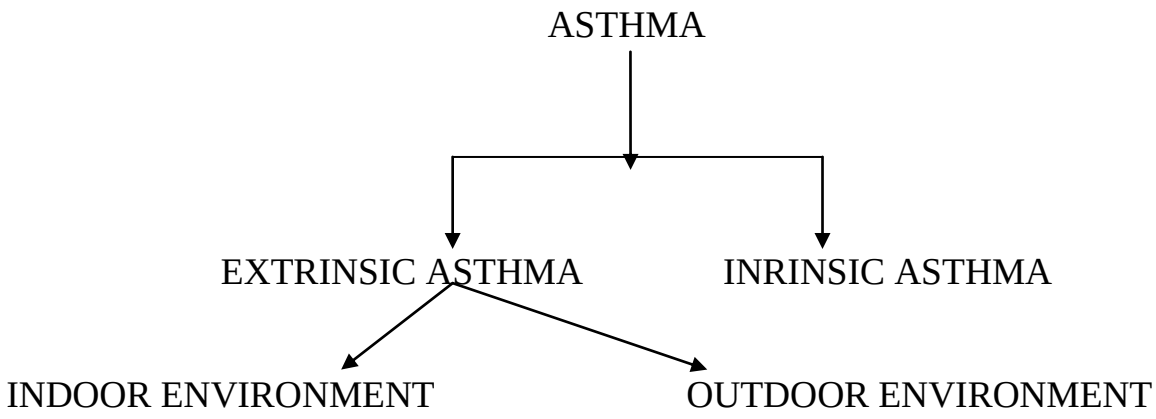
1)positive family history of atopy 2)low/high birth weight 3)prematurity 4)maternal smoking during pregnancy 5) high intake of salt 6) pet ownership 7)childhood viral infection 8)obesity[14]

ATOPY AND ASTHMA:

Amongst these risk factors family history of atopic disease is the strongest of all risk factors [15]. Increase in the risk of developing allergic rhinitis is fivefold and the risk of developing asthma is threefold to fourfold in a person with family history of atopy[16] . In children, both positive skin tests and increases in total serum IgE are strongly associated with asthma [17]. Serum IgE correlates strongly with bronchial hyperresponsiveness[18].

Asthma may be categorised as follows [19]

Figure 1: Classification of asthma



EXTRINSIC ASTHMA**:**

It is due to the response of the immune system to inhaled allergens such as pollen, dust particles, animal dander, ozone (OUTDOOR ENVIRONMENT) or house mite, cats, dogs, molds. (INDOOR ENVIRONMENT).

Exposure to mite in the household increases the risk of developing asthma in a dose dependent manner [20] . A modest control of mites in the household reduces the incidence of asthma up to 8 years of life [21].

INTRINSIC ASTHMA:

It is due to the response of immune system, to nicotine and other chemicals inhaled while smoking cigarette, to emotional factors like laughter and stress and when on NSAIDs particularly aspirin intake.

HYGIENE HYPOTHESIS**:**

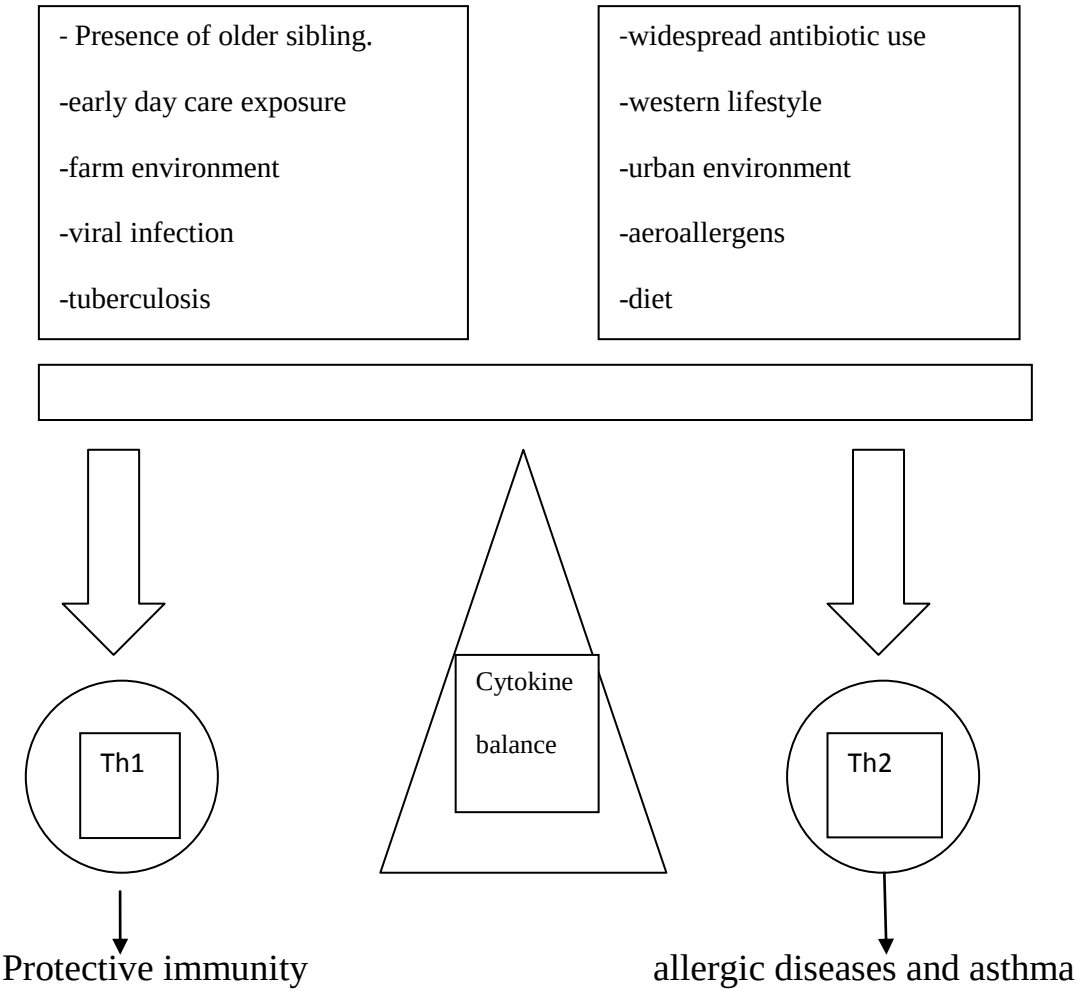
The most exciting theory proposed for explaining the early childhood infection as a protective factor in preventing asthma is the “hygiene hypothesis." It states as

“***The rise in allergies in children is an unintended consequence of the success of domestic hygiene in reducing the rate of infections in early childhood”.***

Thus according to this theory the more the hygienic practice, the more the medical and social changes and the smaller the family size becomes, less is the chance of childhood infections in the population and the chances of developing asthma increases especially in those with family history of atopy. Possible explanation for this hypothesis is immune selection through which the Th2 cells are selected over the Th1 cells (normally predominant) in the mucosal surfaces.

The immunologic milieu at the fetal—maternal interface is towards a Th2 phenotype, and this immune bias is carried into neonatal life[22]. Unless the pattern of immune response in the airways is "reprogrammed" toward a Th1 pattern, the infant will have a prolonged high-risk window for allergic sensitization to aeroallergens[23]. The principal impetus to this reprogramming of the mechanisms of the immune response toward a normal Th1/Th2 balance is hypothesized to be contact with pathogenic and commensal microorganisms at the body's mucosal surfaces [24].

Figure 2: Factors determining asthma development



VIRAL RESPIRATORY TRACT INFECTIONS AND ASTHMA:

That viral infection of the airways might have a role in inducing asthma. Childhood history of bronchiolitis was a major predictor of airway hyper responsiveness and allergic sensitivity later in life [25]. Upper respiratory infections (URIs) were noted to occur 1 to 2 months prior to the onset of allergic sensitization in most of the children according to a large longitudinal study [26]. The number of URIs in infancy is inversely related to the risk of asthma, but it is exactly the opposite with the lower respiratory tract infection [27] . The most common causative organism associated with respiratory tract infection in the childhood period is Respiratory Syncytial Virus. RSV has been suspected of having unique effects on the infant respiratory tract favouring allergic sensitization and asthma [28]. The strongest correlate of wheezing before age 3 is small airway calibre, whereas wheezing after age 3 correlates with elevated serum IgE and a maternal history of asthma [29].

OTHER MICROBIALS IN ASTHMA:

Chlamydia pneumoniae and *Mycoplasma pneumoniae*, causing atypical pneumonia, infect the airway epithelium and stimulate local inflammatory reactions [30]. They may worsen asthma in those who have the disease or induce it in those with some predisposing condition.

Chronic infection with the above organisms has important association with chronic severe asthma in adults. Significant IgA antibody titre against *C. pneumoniae* was strongly associated with asthma severity [31] . Presence of IgG

antibodies was associated with a fourfold greater rate of decline in FEV_1 in another [32].

OROFAECAL INFECTIONS AND ASTHMA:

Infection with intestinal microbes namely the *Toxoplasma gondii, Helicobacter pylori,* hepatitis A during infancy and childhood were found to have a higher association with protection against the atopy as compared with infections with respiratory pathogens (measles virus, varicella zoster, HSV, CMV and mumps virus). The possible explanation is that following exposure to these organisms there is a immune deviation in the gut lymphoid tissue. This newer concept has questioned the hygiene hypothesis which states that day care centres are associated with higher respiratory tract infections and thus protection against atopy, but this concept suggests the oro faecal infection as the immunodeviation process of protection against atopy.

The emerging evidence of the possible importance of gut commensals and of gastrointestinal exposure for the induction of tolerance to airborne allergens suggests a possible explanation for the rise in allergic diseases in westernized, developed societies [33]. With fewer siblings and less time spent outdoors in play, the exposure of modern children to the microbial world may be insufficient for the inductive programming of healthy, balanced immune responsiveness. The theory also suggests a strategy for primary prevention of allergic disease. If the microbes responsible are harmless or if

their products can be identified, simply adding them to food may reduce the risk of atopic disease. This approach is already being tested in a birth cohort trial of oral lactobacillus supplementation during the first 6 months of life [34].

DIET AND ASTHMA:

The role of dietary factors is controversial. Diets that lack vitamins(C and A) trace elements like magnesium, selenium, and omega-3 polyunsaturated fats or the diets that have a high salt or omega-6 polyunsaturated fatty acid are found to have an increased risk of developing asthma. Vitamin D deficiency may also predispose to the development of asthma. Obesity is also an independent risk factor for asthma, particularly in women [35].

TOBACCO SMOKING AND ASTHMA:

Tobacco smoking has been an important risk factor in development of asthma both in individuals with and without family history of asthma. Its effect has been described in both active smoking and passive smoking [36]. Tobacco causes its effect more in the children when the mother gets exposed to passive/ active smoking in the antenatal period. Tobacco smoking acts as an initial insult to the mucosal defence which results in infections and alternate activation of the immune system (Th2 lymphocytes). But the major effect of tobacco smoking in

asthma comes through the decline in pulmonary function and increases exacerbations in known asthmatics.

Summing up the hypothesis and concepts detailed above the development of asthma in an individual is directly related to the history of atopy in the family. A number of factors act to modify the atopy and thus determine the phenotypic expression of the disorder. The factors which lead on to the expression and thus disease favouring are low/high birth weight, prematurity, maternal smoking during pregnancy, high intake of salt, pet ownership, obesity.

AIR POLLUTION AND ASTHMA

Air pollutants like sulphur dioxide, ozone, and petroleum particulates, may precipitate asthma symptoms, but their role as etiological agent of the disease is much less certain. The present evidence argues against role for air pollution in asthma, as asthma is no more prevalent in cities with high levels of air pollution. Indoor air pollution may be important and have been proven to be associated with asthma. They include exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. There is evidence to suggest that maternal smoking is a risk factor for asthma.

ALLERGENS

Exposure to allergens particularly inhaled allergens has been found to be a risk factor in sensitization to allergy and asthma. Although this is true the

other way is not true, that is stringent measures in controlling these allergens have not resulted in prevention of asthma in this individuals. Exposure to house mite has been one such example when such exposure occurs in the early childhood. Domestic exposure particularly to cats has been associated with allergic sensitization but if it occurs early in the life it may be of protective value through induction of tolerance.

OCCUPATIONAL EXPOSURE AND ASTHMA:

Occupational exposure to chemical agents and allergens has been considered to be one among the leading causes of asthma in young adults. Over two hundred chemicals have been listed to have been associated with the development of asthma. The important agents among these have been toluene diisocyanate and trimetallic anhydrate. They have been associated with allergic sensitation irrespective of the history of atopy. Exposure to animal allergens in the laboratory has also found significant association with allergic sensitization. Occupational asthma may be suspected when symptoms improve during weekends and holidays.

GENETICS IN ASTHMA:

Asthma is regarded as a "complex" disease. The disease results from gene—environment and/or gene—gene interactions. It is unknown still as to how many genes may be involved in asthma susceptibility and what will be the

strength of their effects. One more possibility is that a large number of genes may have actually involved in a combination for the development of asthma population, but only a small subset of genes may actually result in disease in affected individuals. This possibility would be difficult to detect with any of the used statistical approaches to population genetics.

Several genomic regions have been identified in linkage analyses of asthma:

CHROMOSOMAL REGIONS

1. 5q31–33[37] [38] [39]
2. 11q [40] [41]
3. 12q [42] [43] [44] [45]

Of the loci linked to asthma, the 5q23–31 locus is of particular interest. Several studies have demonstrated that this region contains genes related not only to the diagnosis of asthma [37] but also to elevated plasma IgE levels [46] [47] [48] and bronchial hyperresponsiveness[49] . Among the candidate genes in the 5q23–31 region are the genes for IL-4, IL-13, IL-5, IL-9, the locus control region, and the genes encoding for CD14 and the beta$_2$-adrenergic receptor (β_2AR). Several investigators have demonstrated an integral role for many of these candidate genes in the pathogenesis of asthma, IgE production, and mucus hypersecretion[50][51][52][53]

GENETIC VARIATION

Naturally occurring genetic variants, sequence variants, and polymorphism are an important source of genetic diversity. These variants may come in the form of single nucleotide polymorphisms, repeats, insertions, or deletions. Genetic variants in key regulatory regions (i.e., promoter regions) or in the gene itself may alter the normal biologic function or regulation of the gene. Many sequence variants in asthma candidate genes have been studied and have been found to be associated with asthma or asthma-related phenotype [54] . In addition to polymorphisms, it is evident that patterns of genetic variants, termed haplotypes, within a given gene or across a genetic region may be associated with disease. Haplotypes in the β_2AR gene have been shown to have a pharmacogenetic effect by influencing the response to bronchodilators among subjects with asthma.[55]

The practical application of genetics to diagnosis and management may come through pharmacogenetics, that is, the identification of genetic markers predicting responsiveness to specific therapies. A study demonstrates that there are ethnic-specific differences in the response to albuterol. [56] Preliminary evidence suggests that beta$_2$-adrenergic receptor mutation in the form of polymorphisms may affect the response to bronchodilator treatment using an inhaled beta-agonist. A prospective study suggests that regular use of albuterol may cause a decline in peak flow and an increase in exacerbations in patients

homozygous for Arg/Arg, in contrast to Gly/Gly, at the amino acid 16 position.[57]

ASTHMA TRIGGERS:

Several stimuli trigger airway narrowing, wheezing, and dyspnea in asthmatic patients.

ALLERGENS

Inhaled allergens are mostly associated with the triggering episodes. Among the notable allergens are the *Dermatophagoides species*, allergens from the pets like cats and from insects like cockroaches. These are considered to be perennial allergens causing symptoms throughout the year. Pollens are seasonal allergens associated mainly with allergic rhinitis but they may trigger severe asthma when disrupted in large amounts during thunderstorms (thunderstorm asthma)

VIRAL INFECTIONS:

Infections of the respiratory tract by viruses like corona virus, rhino virus and RSV may exacerbate asthma symptoms.

PHARMACOLOGIC AGENTS:

Non selective beta blockers increase the risk of exacerbation in asthma by increasing cholinergic bronchoconstriction

ASPIRIN SENSITIVE ASTHMA:

This occurs in patients with genetic predisposition for marked production of leukotrienes due to the genetic polymorphisms of the enzyme *cys-leukotriene C synthase*. It is associated with late onset asthma, perennial symptoms and nasal polyps. Happens following exposure to non selective COX inhibitors especially aspirin.

EXERCISE:

Exercise induced asthma occurs in children mostly. It is due to the hyperventilation induced increase in osmolality that imbibes fluid in the airway leading to airway obstruction. The symptoms start soon after exercise and settles spontaneously in 30 minutes.

FOOD AND PHYSICAL FACTORS:

Certain foods containing metabisulfite, a preservative, may trigger asthma. Also shell fish and nuts may trigger asthma as a part of generalised allergic reaction. Physical factors like cold and hyperventilation trigger asthma.

HORMONAL FACTORS:

Premenstrual worsening in women secondary to fall in progesterone levels, thyrotoxicosis and phaeochromocytoma may worsen asthma.

GASRTROESOPHAGEAL REFLUX:

Gastroesophageal reflux is common in asthma as it is increased by bronchodilators. Acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and antireflux therapy fails to reduce asthma symptoms in most patients.

STRESS

Many asthmatics report worsening of symptoms with stress. Psychological factors can induce bronchoconstriction through cholinergic reflex pathways. Paradoxically, very severe stress such as bereavement usually does not worsen, and may even improve, asthma symptoms.

The understanding of the pathology and the pathophysiology of asthma has given us the proper explanation for the transformation of asthma into a irreversible airway disease that almost behaves like COPD. The review of this literature is thus designed in a way to make the understanding of the pathophysiology better with a crisp and brief cover on the management of the disease.

PATHOLOGY

STRUCTURAL CHANGES IN THE AIRWAY

Asthma in its stable form has been characterised by invasion of multiple inflammatory cells in to the airway wall. They along with their inflammatory mediators bring about the pathological consequences like subepithelial collagen deposit along with goblet cell and smooth muscle hyperplasia and angiogenesis leading in to the structural airway changes in asthma.

EPITHELIAL CHANGES:

Epithelial changes described in the pathological features of asthma are epithelial denudation and squamous metaplasia. Of these the debate has been over the inclusion of epithelial denudation as a pathological hallmark of asthma. But studies haven't clearly distinguished whether it is due to the disease per se or due to the artefact created secondary to the sampling.

Squamous metaplasia is a pathological feature of asthma when the epithelium remains to be intact [59] . Goblet cell hyperplasia or hypertrophy is a consistent feature seen in patients with fatal asthma. [60][61] Goblet cell hyperplasia is also seen in mild to moderate asthma [62] . This results in a threefold increase, in the amount of stored mucin in the airway epithelium, which was also associated with up regulation the epidermal growth factor receptor expression (whose activation results in mucin production).[63] Increases

in stored mucin render asthmatic subjects vulnerable to mucin hypersecretion during periods when mucin secretagogue levels rise (e.g., during asthma exacerbations).[64]

EOSINOPHILIC INFLAMMATION:

Increase in the number of activated eosinophils is the pathological hallmark of asthma in the submucosa and airway epithelium. [65] [66] [67] [68] The degree of eosinophilia is highly variable, and relatively few eosinophils were identifiable in the airway tissue in a subgroup of asthmatic subjects. [65] . Eosinophil numbers are often increased in the peripheral blood, but peripheral blood eosinophilia is not as sensitive an indicator of asthma as sputum eosinophilia.[69]

SUBEPITHELIAL CHANGES:

Large amounts of type III and V collagens, along with fibronectin and tenascin are deposited beneath the airway epithelium in the bronchus of asthmatic patients [70] . Myofibroblast that are increased in asthma have been the source of these proteins. [71]

The bronchial blood vessels increase in both number and size in asthma. [72] The vessels are prone to have large volumes which increase the mucosal swelling and narrow the airway lumen [73] . They are also characterised by

vasodilation, vascular permiability, plasma extravasation, and airway mucosal edema. [74][75]

There is a hypertrophy and hyperplasia of airway smooth muscles [76] [77]. Airway cartilage shows degeneration and pericartilaginous fibrosis. [78]

CHANGES IN AIRWAY MUCUS:

Eosinophil lysophospholipase a derivative of eosinophils has been implicated in the formation of Charcot-Leyden crystals .[79][80] . Sheded epithelial cells form the creola bodies. [81] Albumin and DNA,the nonmucin molecules, whose concentrations are increased in asthma,[82][83] reflect abnormal bronchovascular permeability and increased cellular inflammation. The albumin concentrations in sputum in asthma could be important, especially when combined with changes in the mucin concentration. [84]Mucin glycoproteins are the predominant proteins in sputum, and mucin concentrations are modestly increased in asthma as compared to normal individuals. [83] Large amounts of mucus accumulation leads to increased sputum production, cough and airway obstruction that may even precipitate life threatening attacks in asthma[85][86] .

LARGE AIRWAY VERSUS SMALL AIRWAY PATHOLOGY

Pathologic changes at different sites in the tracheobronchial tree in asthma are qualitatively similar irrespective of the airway size and calibre [87] . The degree of subepithelial fibrosis in proximal airways is representative of its

thickness in distal airways. Eosinophilic inflammation extending into the alveolar septa in asthmatic subjects [88] , challenges the notion that asthma is a disease whose pathology is limited to the airway wall. Goblet cell metaplasia may be particularly important as the source of mucus that occludes many small airways because small noncartilaginous airways do not have submucosal glands.

AIRWAY PATHOLOGY IN ALLERGIC AND NONALLERGIC ASTHMA

The pathology of "extrinsic" (allergic) asthma and "intrinsic" (nonallergic) asthma (as judged by skin test reactivity and IgE levels) does not differ.[89] Both forms of asthma are characterized by increases in eosinophils, mast cells, and $CD4^+$ lymphocytes expressing cytokine profiles typical of the Th2 lymphocyte subgroup.[90][91][92]

FATAL ASTHMA

Extensive mucus plugging of the airways, high degree of airway wall thickening with smooth muscle and submucosal gland hypertrophy is typically found in autopsies of asthma fatalities and is considered a major cause of asphyxiation during a lethal attack [93] . The predominant cells in fatal asthma are eosinophils,[94] but neutrophils may also predominate in those who die very quickly after the onset of a lethal attack.[95][96]

RELATIONSHIP BETWEEN AIRWAY PATHOLOGY AND ASTHMA SEVERITY

All of the characteristic findings of asthma are at least qualitatively similar in mild, moderate, and severe asthma, but inflammation and pathology is worse in more severe asthma. Higher eosinophil percentages in induced sputum from asthmatic subjects are associated with lower FEV_1 and heightened sensitivity to methacholine.[97][98]. $FEV_{1\ is}$ inversely associated with genetic expression levels of IL-5 and IL-13 in the airway mucosa. [99][100] . Higher neutrophil percentages are found in induced sputum in patients with more severe asthma, and airway neutrophilia is more strongly associated with lower values of FEV_1 than with greater bronchial reactivity to methacholine.[97]

The pathology of severe asthma shows that more severe disease is associated with increased numbers of airway smooth muscle cells and fibroblasts in the submucosa.[101]

SPECIFICITY OF AIRWAY INFLAMMATION

Chronic obstructive pulmonary disease (COPD), may have an element of eosinophilic inflammation but to a lesser degree than is found in asthma.[102] Similarly, modest increases in airway eosinophilia are found in subjects with allergic rhinitis without history of asthma.[103] Smooth muscle hypertrophy is a feature of chronic bronchitis as well as of asthma.[104] . Mononuclear cell

infiltrates of the airway wall are characteristic of both asthma and chronic bronchitis, but the nature of the mononuclear cell infiltrate differs: in asthma the cells consist predominantly of $CD4^+$ lymphocytes, whereas in chronic bronchitis they consist predominantly of $CD8^+$ lymphocytes [105] . Also, subepithelial fibrosis can be observed in chronic bronchitis and in allergic rhinitis, but the degree is much lower than in asthma. [106]

PATHOPHYSIOLOGY

ORIGIN AND EVOLUTION OF ASTHMA

Based on inflammation within the airways as a main component a hypothesis has been suggested to the natural course of asthma. The mast cell, eosinophil, CD4 lymphocyte and airway epithelial cell have been substrates of the inflammation in asthmatics. The most important of all is CD4 lymphocyte.

Individuals who have a genetic susceptibility for atopy when exposed to specific risk factors in the early life will mount a specific inflammation consisting of Th2 lymphocytes in the airways. This is made possible by intra uterine programming of the fetus with a lesser exposure to infections in the childhood which selectively stimulates the naive Tcells to differentiate into the Th2 cells. With certain viral infections this airway inflammation goes in for exacerbation and thus airway remodelling and worsening of the lung function.

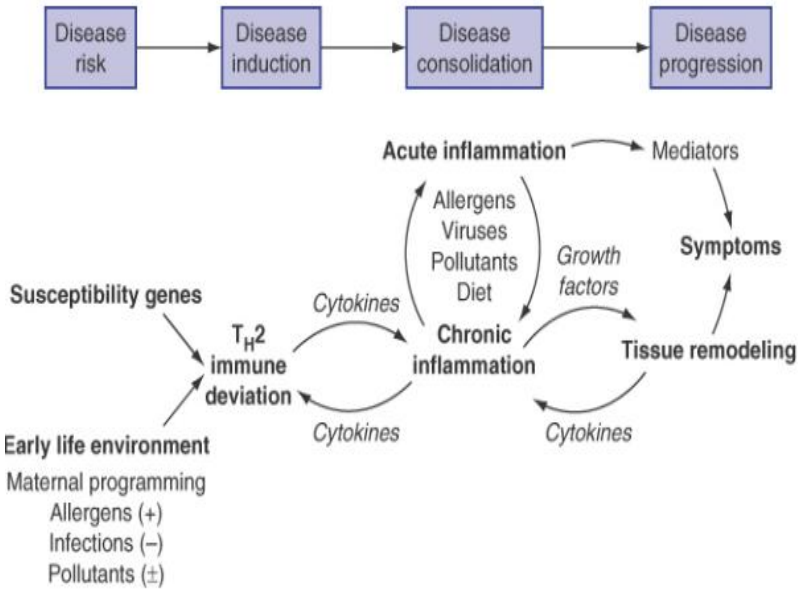


Figure 3:Summary of current hypotheses for the evolution of asthma.[107]

INFLAMMATORY MECHANISM OF ASTHMA:

When an inhaled antigen is encountered by the antigen presenting cells it is first uptaken by these cells and then processed and presented to the naive T cells. These naive T cells differentiate into Th1 and Th2 cells based on the type of cytokines that act on them. IL-3,4,5,6,9,10,13 are the cytokines secreted by Th2 cells and thus brings about asthma expression.

IMMUNE MECHANISMS:

A number of cells, cytokines have been elucidated in the pathophysiology of asthma. Yet only a few have been critical in the development of asthma

phenotype. The noteworthy are as follows, Dendritic Cells, Antigen Presentation, T Cells, Cytokines, Airway Epithelium, B Cells, Mast Cells, Basophils, and IgE , Eosinophils , Neutrophils and Macrophages. A brief description on these cells and cytokines has been mentioned below.

DENDRITIC CELLS, ANTIGEN PRESENTING CELLS, TCELLS AND CYTOKINES

Airway dendritic cells are antigen-presenting, potent at initiating and sustaining airway inflammation. Their density in the airway will increase rapidly upon airway stimulation with allergen. [108] Dendritic cells express co stimulatory molecules that facilitate T-cell activation and differentiation. [109] $CD4^+$ T cells are the principal recipients of antigen presented by dendritic cells. Environmental lipopolysaccharide is important in initiating allergic lung disease.[109] Dendritic cells secrete a number of mediators, which include IL-12, prostaglandin E_2, and IL-10, which critically influence effector $CD4^+$ T-cell development.

The Th2 cells selectively accumulate in the lungs during allergic inflammation[110]. The cytokines that contribute to the asthma phenotype are IL-4 and IL-13. IL-4 functions primarily as a growth or differentiation factor for Th2 cells and promotes IgE secretion by B cells and IL-13 may also promote IgE secretion in humans. IL-10 negatively regulates both Th1 and Th2

cytokines and is critical for maintaining the normal tolerogenic airway immune state and down-regulating allergic airway inflammation. [111]

ROLE OF THE AIRWAY EPITHELIUM

Airway epithelial cell functions well beyond those of barrier protection, mucus secretion, and the mucociliary clearance necessary for host defence [112]. The epithelium responds to inflammatory stimuli by synthesizing biologically active mediators that can moderate the airway inflammation. These mediators include cytokines and chemokines that can influence inflammatory cell trafficking and activation of arachidonic acid metabolites, endothelin-1, nitric oxide, and reactive oxygen species. [113]

Air pollutants, respiratory viruses, aeroallergens, bacterial products, eosinophil and neutrophil granule products, and Th2 cytokines may activate epithelial cells directly or indirectly. [114].Goblet cells of the airway and gut also express a chloride channel (Gob-5) that is essential for mucus hypersecretion and airway hyper responsiveness. [115]

B CELLS, MAST CELLS, BASOPHILS, AND IgE

Type I hypersensitivity reactions are considered an important cause of acute asthma exacerbations and may contribute to chronic airway inflammation in asthma. In these reactions antigen cross-links IgE that are bound to receptors on mast cells or basophils. This activates the cells and thereby release a variety

of products, including histamine, tryptase, chymase, leukotrienes, platelet-activating factor, and various cytokines (IL-4, IL-5, TNFα) that in turn promote airway hyperresponsiveness, mucus overproduction, fibroblast activation, and neuropeptide degradation. IgE-mediated activation of mast cells and basophils, and IgE-facilitated antigen presentation to T cells are considered important mechanisms of the early-phase and late-phase responses to inhaled allergen [116].

EOSINOPHILS

Eosinophils secrete inflammatory mediators like granule proteins, proteolytic enzymes, lipid mediators, oxygen metabolites, and cytokines. These mediators directly or indirectly cause airway narrowing, airway hyper reactivity, and mucus hyper secretion. Eosinophil numbers increase dramatically in the airways of asthmatic subjects 4 to 24 hours following an aerosolized allergen challenge,[117] and their appearance coincides with the development of late-phase asthmatic responses[118] . Eosinophil numbers increase in airway secretions during asthma exacerbations induced by corticosteroid withdrawal[119] . Eosinophils are prominent in secretions and in the airway wall in fatal cases of asthma. Airway eosinophilia coincides with asthma severity. The action of corticosteroids in asthma are hypothesized to result at least in part from the eosinophilopenic effects of these drugs.[120]

NEUTROPHILS

Neutrophil numbers are increased in secretions and biopsies in both acute severe asthma and chronic severe asthma [121]

Neutrophil elastase, cathepsin G, and proteinase 3 are secreted by neutrophils and are important mediators of goblet cell and submucosal gland cell degranulation.[122] . Neutrophils may potentiate asthma, particularly acute exacerbations, by inducing mucin hypersecretion and possibly by increasing bronchovascular permeability. The abnormal accumulation of neutrophils in the airways during acute exacerbations may be mediated by IL-8 secretion from airway epithelial cells activated by virus or antigen exposure. [123]

MECHANISMS OF LEUKOCYTE RECRUITMENT TO AND EGRESSION FROM THE AIRWAY

Selectins, expressed on leukocytes, bind to their ligands on endothelial cells to initiate tethering and rolling, which is the first step in endothelial transmigration. Tethering and rolling is followed by firm adhesion mediated by integrins. Chemotaxis is the final step in inflammatory cell recruitment.

Egression of inflammatory cells, a step in the resolution of inflammation, involves establishment of appropriate chemokine gradients. Matrix metalloproteinases (MMPs) regulated chemokines allow egression of allergic inflammation, especially MMP2. [124]

MACROPHAGES

Macrophages may be involved in both the induction and effector phases of immune responses in asthma. In the induction phase, macrophages function in several ways, including the uptake, processing, and presentation of antigens and the secretion of immunostimulatory hormones.[125] In the effector phase, macrophages function as cytotoxic cells and also as effector cells capable of secreting a wide variety of pro-inflammatory mediators including cytokines, arachidonic acid metabolites, and proteases.[126]. Studies have demonstrated that the beneficial effects of corticosteroids in asthma may be mediated at least in part by down-regulation of alveolar macrophages.[127]

Hypotheses have been proposed claiming failure of macrophage-mediated T-cell regulation to be an important factor in T-cell proliferation and activation in asthma. [128]

Only those allergens that possess protease activity (example: pollen, fungi) are capable of inducing allergic lung disease.

EFFECTS OF AIRWAY INFLAMMATION:

- Epithelial damage and shedding (contributes to airway hyperresponse).
- Subepithelial fibrosis (contributes to non elastic irreversible airways).
- Smooth muscle hypertrophy causes narrow airway.

- Angiogenesis, micro vascular leakage and mucosal edema.
- Mucus hypersecretion and accumulation leading to exacerbations.
- Bronchoconstriction secondary to cholinergic stimulation

AIRWAY REMODELING

Airway remodeling in asthma may have at least three distinct consequences.

1. Even moderate increase in airway thickening will markedly increase the airway narrowing and worsens the scenario following smooth muscle contraction.[130]
2. The airway wall thickening is the reason behind the persistent and irreversible airflow limitation in some patients with asthma.[131]
3. Increased blood flow with hyperplasia of goblet cell causes increase in mucus secretion leading on to mucus plug formation and precipitation of exacerbation[132]

Hyperpolarized helium-3 is a gaseous contrast agent that provides a new technique for magnetic resonance imaging in asthma. Studies have shown that this method can detect methacholine-induced bronchoconstriction[133] and it may prove useful for assessing the effects of treatment on airway narrowing secondary to remodeling.

PHYSIOLOGIC DISTURBANCES

The functional disturbances are most clearly seen during severe attacks. All physiologic consequences derive from narrowing of the airways. There is diffuse narrowing of the whole trachea and bronchi but the maximum narrowing occurs in bronchi of diameter between 2 to 5 mm.[134]

Tests of airway function are abnormal. There are a following pattern of spirometric tests that are characteristic of airflow obstruction.

1. Increased airway resistance and reduced Maximum expiratory flow rates. Maximal inspiratory flow is also reduced but less so.
2. Narrowing of peripheral airways results in their premature closure at higher lung volumes, and increase in residual volumes [135].
3. Increase in the functional residual capacity is due to i)the inability of the lungs to empty during the expiratory phase of the respiratory cycle because of the high resistance to expiratory flow[136] ii)another is a sustained increase in the activity of inspiratory muscles even during expiration.[137]
4. The adaptive advantages of breathing at higher lung volumes are increases in the circumferential traction—or "tethering" force—on intrapulmonary airways, tending to hold them open, and an increase in the elastic recoil of the lungs, increasing the driving pressure for

expiration. These adaptive gains are partially offset by a decrease in lung elastic recoil in acute, severe asthma.[138]

5. The increased resistive work due to narrowing of airways and the increased elastic work due to reduced lung compliance with high thoracic cage volume leads to increase in work of breathing. This increased work must be performed by muscles of breathing placed at a mechanical disadvantage by overinflation of the thorax.
6. At high thoracic volumes, the diaphragm and intercostal muscles must function over a suboptimal range of their length-tension curve, and accessory muscles (e.g., the sternocleidomastoids) are brought into play.[139] The increase in the work of breathing causes fatigue, and the inappropriateness of the length-tension relationship in the muscles of breathing is perceived as dyspnea.

PHYSIOLOGICAL DISTURBANCES IN ACUTE SEVERE ASTHMA:

The airway narrowing of asthma affects gas exchange. The severity of obstruction is not uniformly distributed. Shifts in pulmonary blood flow cannot completely compensate for the under ventilation of the regions of lung subtended by the most obstructed airways. The resulting mismatch of ventilation to perfusion widens the alveolar-arterial oxygen difference [(A - a) P_{O_2}], and arterial oxygen tension in patients with acute severe asthma typically ranges between 60 and 69 mm Hg.[140] The hypocapnia is caused by

hyperventilation done by stimulation of neural receptors supplied by afferent fibers in the vagus nerves. This increased respiratory drive is almost invariable in acute asthmatic attacks. An elevated or even normal arterial P_{CO_2} is a sign of severe airflow obstruction where there is a mismatch between muscles of respiration and the respiratory centre [141]

Alveolar ventilation falls suddenly with any worsening of airflow obstruction, any loss in muscle performance (as from fatigue), or any decline in respiratory drive (as from administration or a narcotic or sedative drug). This raises the Pco2 and inhibits the muscle performance and respiratory drive (*carbon dioxide narcosis*) which if left untreated leads to respiratory failure and death. [142] Hypercapnia indicates severe exacerbation, which requires aggressive treatment with bronchodilators and preparation for possible intubation and mechanical ventilation.

Severe airflow obstruction usually improves quickly with treatment but resolves entirely much more slowly. When symptoms have resolved, FEV_1 and residual volume still average 50% and 200% of normal, respectively. Even when wheezing has resolved and the physical examination is entirely normal, maximal expiratory flow is still markedly reduced, especially at mid and low lung volumes and residual volume remains increased.

PULMONARY FUNCTION TESTING

Pulmonary function testing can be done both clinically and mechanically. The gold standard method used in measuring the lung volumes is spirometry.

CLINICAL METHODS:

1) Duration of the expiratory phase heard on auscultating over the trachea - >6 sec obstructive
2) Single breath count test-normal 35-40
3) Candle blowing test at 15 cm

SPIROMETRY:

Spirometry is a simple test that measures various lung volumes with the active patient's effort of breathing. It is performed using a machine called spirometer. There are two types of spirometer. Volume-displacement and flow sensing spirometers. Flow sensing spirometers have largely replaced volume displacement spirometers.

Pulmonary function testing performed between attacks, or even after long periods of remission of asthmatic symptoms, usually shows characteristic changes. The easiest to detect are reductions in maximal expiratory flow. Calculation of peak flow variability(the difference between the AM and PM values divided by the mean of the two) can also be used for detecting abnormal airway lability, as an indirect measure of bronchial responsiveness[143].

The volume of air expired during the first second of a forced expiratory manoeuvre from total lung capacity (FEV_1) is the best-standardized, most widely used test for airflow obstruction. ***An improvement in FEV_1 of more than 12% and more than 200 ml after administration of a bronchodilator is a hallmark of asthma.***[144] Interpretation of the FEV_1 requires simultaneous measurement of the forced vital capacity (FVC), the total volume exhaled from total lung capacity (TLC) to residual volume. Usually the reduction in FEV_1 is more than the reduction in FVC, so the FEV_1/FVC ratio is typically low in asthma. An exception is severe asthma, in which residual volume may be so increased that the reduction in FVC is proportional to the reduction in FEV_1. Conversely, treatment may reverse narrowing of peripheral airways, allowing exhalation of a greater volume before airway closure occurs, so the improvement in FVC can be proportionately greater than the improvement in FEV_1.

An index derived from the FVC is the maximum mid expiratory flow, or the forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75\%}$), the mean rate of flow over the middle half of the vital capacity. Flow over this lower lung volume was thought to be more precise for small airway obstruction than the FEV_1,[145] and a normal $FEF_{25–75\%}$ value indeed makes asthma unlikely[146] but not impossible.

An alternative to measuring FVC is measurement of the volume of air expired over the initial 6 seconds of a forced expiratory maneuver, the FEV_6 [147]. This manoeuvre is less demanding on patients and equipment and virtually never leads to misclassification of disease or disease severity based on the FVC.

TABLE 1: COMPARISON OF RESPIRATORY PATHOLOGIES USING SPIROMETRIC RESULTS

	OBSTRUCTIVE	RESTRICTIVE	MIXED
FEV_1	↓	↓ OR NORMAL	↓
FVC	↓ OR NORMAL	↓	↓
FEV_1/FVC	↓	↑ OR NORMAL	↓

Although above table can be used easily to interpret the obstructive and restrictive pattern differentiating asthma and COPD among the obstructive diseases using spirometry has limitations. They are as follows:

1. The absence of reversibility does not exclude asthma as the asthmatic person's response can vary from time to time and at times airway calibre in asthmatic subjects is absolutely normal and as not capable of dramatic improvement.

2. FEV_1 may improve significantly after bronchodilator and a change of >12% and > 200 ml in FEV_1 can occur in COPD [148].
3. In long standing bronchial asthmatics the airway remodelling may cause irreversible airflow obstruction and thus mimic COPD in picture.
4. In India there has not been a wide spread practice of establishing the diagnosis of new onset asthma using spirometry making it a diagnosis only on the grounds of history.

Therefore those patients presenting after a long duration of disease treated as asthma have severe airflow impairment which mimic COPD failing to qualify for the reversibility of airflow limitation following bronchodilator.

TESTS OF AIRWAY RESPONSIVENESS

Airway responsiveness is assessed by delivering progressively increasing doses of a provocative stimulus until a chosen index of airway caliber changes by a fixed amount. The stimulus used is methacholine, delivered as a nebulized aerosol in doubling concentrations at 10-minute intervals until FEV_1 falls by more than 20%. The provocative concentration causing a 20% fall is calculated by interpolation and is expressed as the PC_{20}

Airway hyperresponsiveness, defined as a PC_{20} of less than 8 mg/mL, is classically seen in asthma. But this may also be found in other disorders, such *as COPD, cystic fibrosis, and allergic rhinitis*. The degree of responsiveness roughly correlates with the severity of the asthma. [149]

These agents activate the mechanisms responsible for the bronchoconstriction caused by irritants inhaled in ordinary life. A promising "indirect" agent for use in clinical practice is mannitol, which acts locally as the airway mucosa as a hypertonic stimulus. It is prepared in capsules of increasing strength, so serially increasing doses can be easily delivered from a handheld device. [150]

CLINICAL FEATURES

HISTORY

The cardinal symptoms of asthma are wheezing, chest tightness, and shortness of breath. These symptoms are often precipitated by exercise, exposure to allergens, or viral respiratory infections. Variability from day to day with symptoms worsening at night is almost characteristic. [151] Others report variations in symptoms over minutes, and a few even have sudden severe attacks after long periods without symptoms.

COUGH VARIANT ASTHMA:

This form of asthma has been recognized in which wheezing and chest tightness are absent, and exertional dyspnea or cough is the sole presenting symptom. [151] .As many as 30% to 50% of patients with chronic cough have unrecognized asthma. This variant of asthma is more common in children, but 13% of cases of cough-variant asthma occur in adults over 50 years of age. [152]

The cough associated with asthma is typically non-productive, nocturnal, and chronic, sometimes persisting for several years. It is worsened by the same stimuli that worsen the classic symptoms of asthma: exercise, inhalation of cold air, allergen exposure, and upper respiratory infections. [153] Relief is often prompt after initiation of appropriate bronchodilator and anti-inflammatory therapy.

FAMILY HISTORY:

Family history suggestive of allergic rhinitis, atopic dermatitis, or eczema increases the likelihood of a diagnosis of asthma.

HISTORY REGARDING SEVERITY:

The symptoms described by people with asthma are often so characteristic that a strong likelihood of asthma can be established by the medical history alone. The next task is to obtain information about the condition's severity. The features of *fatality prone asthma*, include a history of two or more emergency department visits or a hospitalization for asthma in the past year, the need for intubation and mechanical ventilation for any previous attack, a history of extremely rapid progression of symptoms, [154] and a history of anaphylactic sensitivity to certain foods, such as nuts or shrimp. For all patients with asthma, especially for those with adult onset asthma and nasal polyps, specific questions should be asked about the effects of ingesting aspirin

or foods likely to contain sulphites (dried fruits, restaurant salads, some wines and beers). Both aspirin and sulphite ingestion can provoke severe, life-threatening attacks in patients who otherwise have features of mild or moderate asthma.[155]

Information about exposures to agents known to worsen asthma in the home or workplace, such as pets, cockroaches, house dust mites, and environmental tobacco smoke must be obtained. Questions should be directed toward conditions that complicate or aggravate asthma, such as allergic rhinitis, chronic sinusitis, or gastroesophageal reflux.

PHYSICAL EXAMINATION:

The most characteristic finding of asthma is polyphonic expiratory wheezing, thought to reflect turbulence of airflow in peripheral airways. Wheezing is the first physical finding detected as airflow obstruction progresses, but its absence does not indicate the absence of airflow obstruction. As a reflection of turbulence of airflow, wheeze requires respiratory effort. Wheezing may thus be faint or inaudible in patients making little effort to move air. At the other extreme, the wheeze produced with rapid, forced exhalation does not correlate with airflow obstruction or with bronchial hyper responsiveness. [156]

The other physical findings of asthma are also reflections of airflow obstruction. Over inflation of the thoracic cage may be obvious, resulting in part from the air trapping caused by narrowing of peripheral airways and in part from the adaptive response of breathing at high lung volumes where lung recoil and airway calibre are greatest.

Examination of nonthoracic organs often provides important diagnostic information. Swelling and pallor of the nasal mucosa suggest allergic rhinitis. Nasal polyps, especially in a patient with adult-onset asthma, suggest an increased risk of aspirin sensitivity. [157]

LABORATORY STUDIES

1. Widespread but reversible narrowing of the airways.
2. Increased bronchial responsiveness to inhaled stimuli.

Obstructive pattern demonstrated in spirometry with FEV_1 reversibility is almost suggestive of asthma. Reduction in maximal expiratory flow is a nonspecific finding.

Measurement of bronchial responsiveness presents several advantages as a diagnostic test. Bronchial hyper responsiveness is nearly ubiquitous in patients with asthma, and its degree correlates with the severity of the disease. It is thus highly sensitive; the absence of bronchial hyper responsiveness should stimulate close re-examination of the grounds for suspecting asthma and consideration of

other possible diagnoses. Its major disadvantage is that it is nonspecific. Bronchial hyper responsiveness is found in some patients with chronic obstructive bronchitis and allergic rhinitis.

Chest X-ray may show over inflation of the lungs, bronchial wall thickening, and mucus plugs.

Elevation in serum IgE levels, positive skin prick tests to common antigens, and blood eosinophilia demonstrate the atopic diathesis associated with asthma but do not confirm the diagnosis of asthma.

The association of eosinophilia, high serum levels of IgE, and changing pulmonary infiltrates in a patient with recurrent asthma, especially asthma associated with cough productive of plugs of mucus, should raise suspicion of allergic bronchopulmonary mycosis. [158]

Induced sputum from asthmatics contains a higher percentage of eosinophils and higher concentrations of eosinophilic cationic protein than do samples from healthy subjects.

Measurement of exhaled NO (eNO) is promising for diagnosis and treatment is easy to measure in children; and in children with asthma, eNO correlates with eosinophilic inflammation and airway responsiveness.[159]

TABLE 2 :DIFFERENTIAL DIAGNOSIS

Category	Examples
Diseases causing recurrent episodic dyspnea	Chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, pulmonary emboli, recurrent gastroesophageal reflux with aspiration, recurrent anaphylaxis, systemic mastocytosis, carcinoid syndrome
Common diseases causing cough	Rhinitis, sinusitis, otitis, bronchitis (chronic or postviral), bronchiectasis, cystic fibrosis, pneumonia, diffuse pulmonary fibrosis
Common diseases causing airflow obstruction	Chronic obstructive bronchitis and emphysema, bronchiolitis obliterans, cystic fibrosis, organic or functional laryngeal narrowing, extrinsic or intrinsic narrowing of trachea or major bronchus.

Distinguishing asthma from chronic obstructive bronchitis has been made difficult by the recognition that unremitting airflow obstruction may develop in patients with asthma,[160]especially in those who smoke.[161] For individual patients, the important question is whether the airflow obstruction is

likely to reverse with therapy. **Reversibility is best determined directly, with a trial of corticosteroid and bronchodilator therapy.**[162]

ASTHMA SEVERITY

Clinically asthma has been classified to categorise the patient's severity at the time of diagnosis and for further follow up during therapy. [163]

TABLE 3 : CLASSIFICATION OF ASTHMA SEVERITY

	intermittent	Mild persistent	Moderate persistent	Severe persistent
Daytime symptoms	< 2/week	>2/week not daily	daily	Continuous
Night time symptoms	<2/month	3-4/month	>1/week	Nightly
Activity limitations	none	minor	some	extreme
Reliever medications	< 2/week	>2/week not daily	daily	frequent
FEV_1orPEF	>80%	>80%	60-80%	<60%
Exacerbations	0-1/year	>2/year	>2/year	>2/year

Presence of just one of the feature will place the individual in the grade. The individual is also placed in the highest grade satisfied by him.

SPECIAL FORMS OF ASTHMA

This includes steroid dependent and resistant asthma, difficult asthma, aspirin sensitive asthma and exercise induced asthma. Aspirin and exercise related asthma have been discussed previously.

STEROID-DEPENDENT ASTHMA

This category includes patients who require continuous or frequent treatment with an oral glucocorticoid. The patients who continue to do poorly despite expert management may include those with *steroid-resistant asthma*, as defined by the failure of 2 weeks of treatment with 40 mg methylprednisolone to cause 15% improvement in FEV_1.[164]

SEVERE ASTHMA [165]

This classification includes asthma prone to recurrent sudden attacks, or *brittle asthma*, as well as asthma that rarely cause severe exacerbations but that regularly interferes with sleep, exercise tolerance, or the ability to work, study, or play. Ratings of asthma severity are often based on responsiveness to treatment, rather than on any feature inherent to the disease. Most asthma is well controlled by low doses of an inhaled corticosteroid, and in clinical practice difficult-to-treat asthma (i.e., poorly controlled by inhaled corticosteroid therapy) is considered severe. Possible distinguishing features of this group are neutrophilic (in contrast to eosinophilic) inflammation of the airway mucosa, [166] greater preponderance of females, aspirin sensitivity, and lower level of atopy. [167]

ASTHMATIC BRONCHITIS

The term, asthmatic *bronchitis* is used in two senses. One sense refers to the coincidence of asthma and chronic obstructive bronchitis in a cigarette smoker. Again, there are no formal criteria for this subcategory of asthma, but the usual features are recurrent dyspnea and wheezing, chronic productive cough, and airflow obstruction that are partially, but not completely, reversible with treatment. Overlap between asthma and chronic obstructive disease is common. The ***Dutch hypothesis*** has even proposed that the mechanisms responsible for asthma predispose to the development of COPD, [169] and the rate of decline in FEV_1 is indeed faster in smoking asthmatics than in nonsmoking asthmatics or in healthy smokers. [170] The other sense of asthmatic bronchitis refers to episodes of prolonged production of cough and sputum purulence that often follow viral respiratory infections in asthmatic patients.

ACUTE SEVERE ASTHMA

This is a life threatening condition in asthma. It is characterised by sudden worsening of the patient condition and severe breathlessness that does not resolve on regular doses of short acting inhaled bronchodilators. Acute severe asthma has been classified into 3 categories by the Global Initiative for Asthma. This classification has been used for managing the acute severe asthma.

TABLE 4 : CLASSIFICATION OF ASTHMA EXACERBATION SEVERITY

	Moderate	Severe	Impending Respiratory Arrest
FEV_1 or PEF predicted or personal best	40-69%	<40%	25% or unable to measure
Symptoms	Dyspnea with talking	Dyspnea at rest	Severe dyspnea
Exam	Expiratory wheeze	Inspiratory and expiratory wheeze	Wheeze may become absent
	Some accessory muscle use	Accessory muscle use Chest retraction	Accessory muscle use with paradoxical diaphragmatic movement
		Agitation or confusion	Depressed mental status
Vitals	RR < 28/min	RR > 28/min	Same as severe but could develop respiratory depression and/or bradycardia
	HR < 110	HR > 110	
	O_2sat > 91%	O_2sat < 91%	
	No pulsus paradoxus	Pulsus paradoxus > 25 mm Hg	
$PaCO_2$	Normal to hypocapnic	>42 mm Hg	Hypercapnea is a late sign

MANAGEMENT

PHARMACOLOGIC THERAPY

FIGURE 4: CLASSIFICATION OF ASTHMATIC MEDICATIONS

MEDICATIONS FOR ASTHMA

SHORT TERM RELEIVERS	LONG TERM CONTROLLERS
Beta $_2$ agonists	oral/inhaled corticosteroids
Anti cholinergics	Leukotriene antagonists
Methyl xanthines	mast cell stabilisers
↓	↓
RELAXES AIRWAY SMOOTH MUSCLE	ANTIINFLAMMATORY ACTION

FIGURE 5 : DIAGRAM OF INHALER

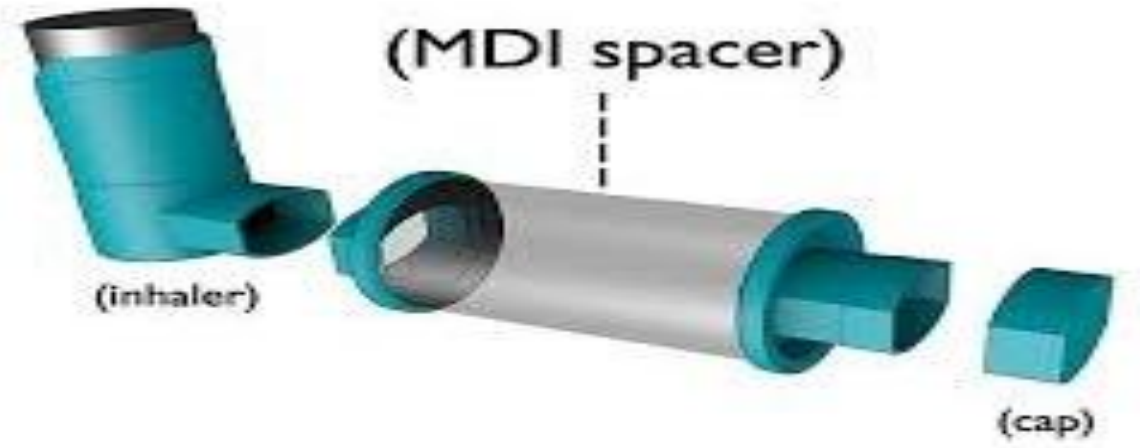


FIGURE 6 :TREATMENT ALGORITHM FOR ASTHMA EXACERBATION

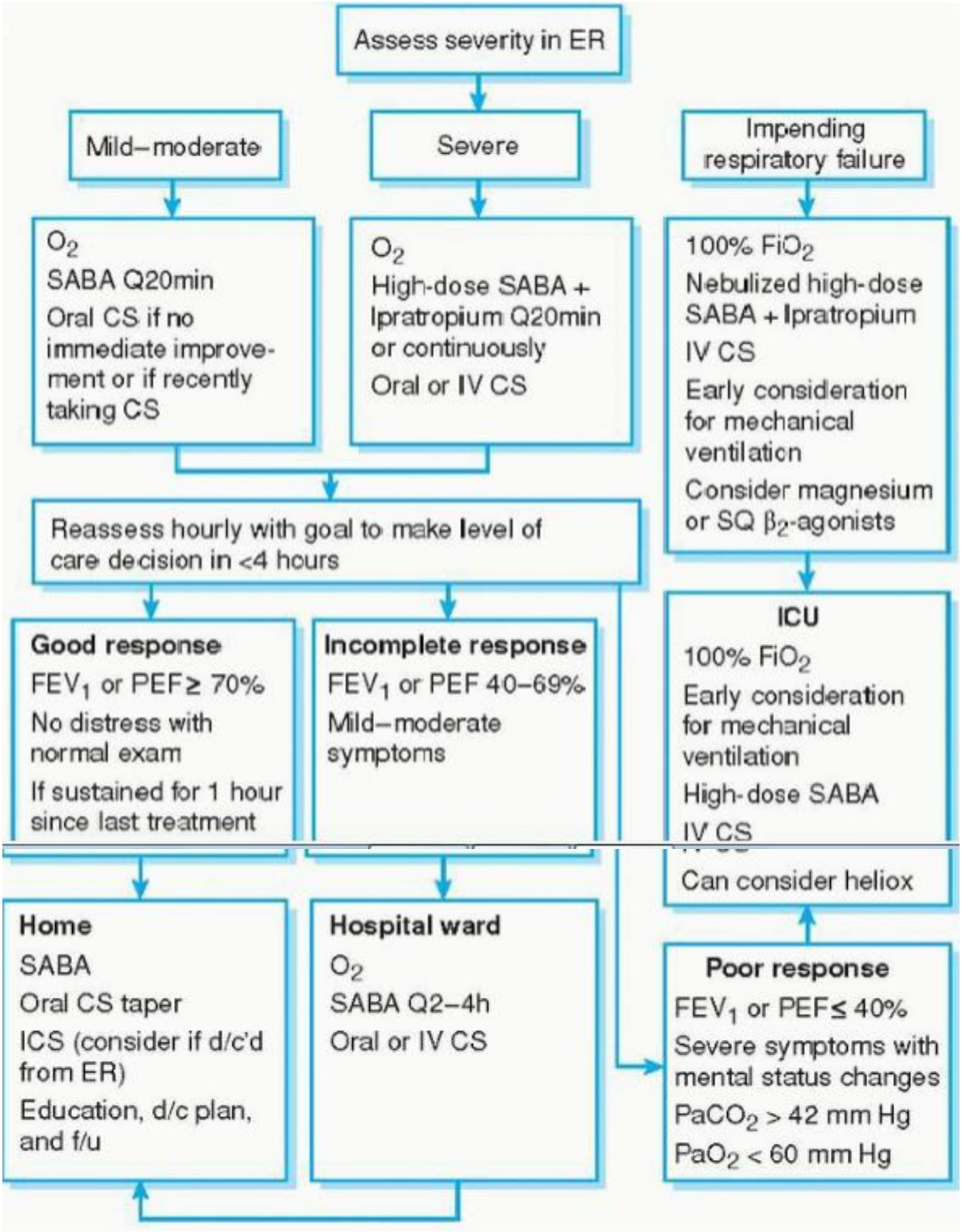


TABLE 5 : STEPWISE APPROACH IN ASTHMA MANAGEMENT

Step 1 Mild, Intermittent	**Step 2 Mild, Persistent**	**Step 3 Moderate, Persistent**	**Step 4 Severe, Persistent**
Quick relief			
Short-acting inhaled β_2-agonist as needed for symptoms	Short-acting inhaled β_2-agonist as needed for symptoms	Short-acting inhaled β_2-agonist as needed for symptoms	Short-acting inhaled β_2-agonist as needed for symptoms
Long-Term Control			
Daily medications not necessary	Daily medications:	Daily medications:	Daily medications:
	Low dose ICS	**Low- to medium-dose ICS + LABA**	**High-dose ICS + LABA**
	or	*or*	
	Cromolyn, nedocromil	Medium-dose ICS	Plus, if needed: systemic corticosteroids
	or	*or*	
	Theophylline	Low- to medium-dose ICS + sustained-release theophylline	Addition of a third controller medication has not been adequately studied
	or	*or*	
	Leukotriene inhibitors	Low- to medium-dose ICS + leukotriene modifier	

IS BRONCHIAL ASTHMA A FORERUNNER OF COPD?

By definition asthma is a reversible airway obstruction and COPD is irreversible airway obstruction involving the airway mucosal inflammation. Although there are other investigational differences like the predominant cells in the airway mucosa (CD8 lymphocytes in COPD and eosinophils in asthma), the size of airways involved (small airways in COPD and medium sized bronchi in asthma),parenchymal destruction(in COPD) , they do not make up much for the clinical use. Therefore by and large the reversibility of the airway obstruction has been the clinical modality of differentiating COPD and bronchial asthma. But during the natural course of asthma the inflammatory process causes airway remodelling, reduced response to beta agonists by alteration of beta agonist receptors, thus leading on to a persistent airflow obstruction that does not respond to the therapies.

Both in the COPD and asthma the predominance of neutrophils are seen at the time of exacerbations and thus this inflammatory cell has been postulated for the development of the irreversibility of the airflow obstruction in these patients. During an exacerbation the mucus hyper secretion and reduced mucus clearance will cause accumulation of mucus plugs in the smaller airway and thus propagating small airway inflammation [177] in them. This has been attributed to the progression of the disease into irreversible state. As the number of exacerbations/ year increase the inflammatory process hastens up and leads to a faster remodelling of the airways and progresses to irreversibility.

Studies have pointed certain factors that are operational in bringing about irreversible airflow limitation in asthma. They are the duration of asthma[172], Male sex, nasal polyps, asthma severity[173], age of onset of asthma[174], number of exacerbations a year[175],sputum eosinophilia.

All the above factors bring about the progression of asthma into a irreversible airway disease and thus transforming it into COPD[176].

AIM OF THE STUDY

AIM OF THE STUDY

- To study the prevalence of irreversible air flow obstruction in chronic asthmatics using spirometry.

- To assess the risk factors contributing to the development of irreversible airflow obstruction in chronic asthmatics.

MATERIALS AND METHODS

METHODS AND MATERIALS

This study was planned to find out the prevalence of a certain objective in a particular population. The study design used is descriptive study. The study was started after obtaining the approval from the ethical committee.

The study was conducted in Government Royapettah Hospital in the department of Internal Medicine between April and October 2013. The target study population was planned as fifty cases.The study was conducted after formal informed consent from the patients.

INCLUSION CRITERIA:

Patients who were aged more than 18years with a asthma duration >10 years.

EXCLUSION CRITERIA:

- Active respiratory tract infection
- Patients with active or old history of tuberculosis
- Patients treated as COPD
- Asthmatic patients who met hospitalization criteria.
- Patient with complaints of hemoptysis
- Recent MI (1 month)
- Recent stroke, eye surgery, thoracic/abdominal surgery
- Recent pneumothorax
- Uncontrolled hypertension
- Active gastric ulcer/UGI bleeding
- Patients who are hemodynamically unstable.

- Patients who have a smoking history starting before/concurrent with the onset of symptoms (breathlessness).

STUDY PROTOCOL:

The patients attending the asthma clinic and the medicine op for medications were enrolled into the study. After a proper history and physical examination patients who had exclusion criteria were screened. The patients who met the inclusion criteria were advised a complete blood count, chest x-ray, ECG, Sputum analysis. Those patients who had no evidence of respiratory tract infection evidenced by the sputum result and ECG showing no evidence of acute ischemic/ recent infarction changes were chosen for the study.

The patients had their disease defined as asthma by an affirmative answer to the following questions.

- Diurnal variation of symptoms
- Predominantly nocturnal symptoms
- Seasonal aggravation of symptoms
- Presence of nasal polyps
- Allergic tendencies to known allergens
- Positive family history
- Complete relief of the symptom in the past/present with nebulisation
- Normal or near normal activities in between the symptoms.

Those patients categorised as asthmatics were asked to refrain from smoking, coffee, tea and heavy physical activity immediately before the

performance of pulmonary function testing (PFT) using spirometer. The patients were also asked to review after complete cessation of intake of salbutamol, theophylline for more than 48 hrs.

The patients were demonstrated how to perform PFT using spirometer. Flow sensing electronic spirometer which was accurately calibrated was used in this study. A total of 3 readings were taken both before and after bronchodilator nebulisation. Among the three, the well performed reading and the reading with the maximum values was considered.

The cases which demonstrated purely an obstructive pattern in the PFT were analysed for the reversibility of the obstruction. The cases who demonstrated a rise of FEV_1% >12% or 200 ml following salbutamol nebulisation for 20 minutes were considered to have a reversible airflow obstruction. Those who failed to raise their values to above levels were given a trail of 40 mg of prednisolone for two weeks. PFT was performed two weeks later. Those who still did not achieve the above target values were considered to have a irreversible airflow obstruction.

$$FEV_1 \text{ reversibility} = \frac{\text{postbronchodilator } FEV_1 - \text{prebronchodilator } FEV_1}{\text{prebronchodilator } FEV_1} * 100$$

The patients were initially divided into two groups. Those whose symptoms started <12 years where termed as childhood asthmatics and those who symptoms started >20 years were termed as late onset asthmatics.

The results were tabulated and the prevalence rate of irreversible airflow

obstruction among the 50 asthmatic cases was calculated. The distribution of cases between the childhood and late onset asthma was calculated.

Along with this other variables collected were duration of asthma, smoking, use of glucocorticoids, asthma severity, number of exacerbations/year. The number of exacerbations a year was defined by number of hospitalisations required for the symptoms which did not respond to conventional nebulisation. Measurement of smoking used in this study is smoking index which is defined as the number of cigarettes/ beedis per day multiplied by number of years of smoking.

An attempt was made to find out the association of above variables with irreversible airflow obstruction and their statistical significance was calculated using pearson's chi-square tests. The significance of the association was established using the p value.

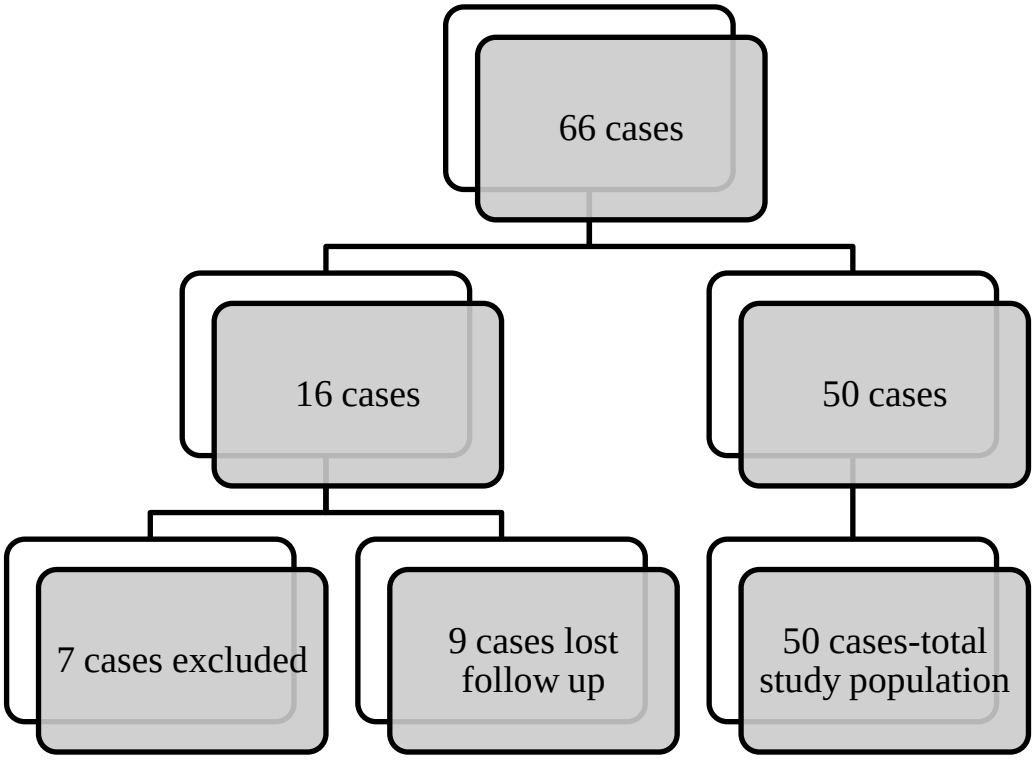
- If the P value is 0.000 to 0.010 it is highly significant.
- If the P value is 0.011 to 0.050 it is significant.
- If the P value is 0.051 to 1.000 it is not significant.

RESULTS

RESULTS

A total of 66 people took part in the study out of which 7 people were excluded as there was an overlap between the age at onset of symptoms and age at which they started to smoke. 9 people did not come for follow up after two weeks steroid trail. Final population under the study was 50.

FIGURE 6: POPULATION UNDER STUDY

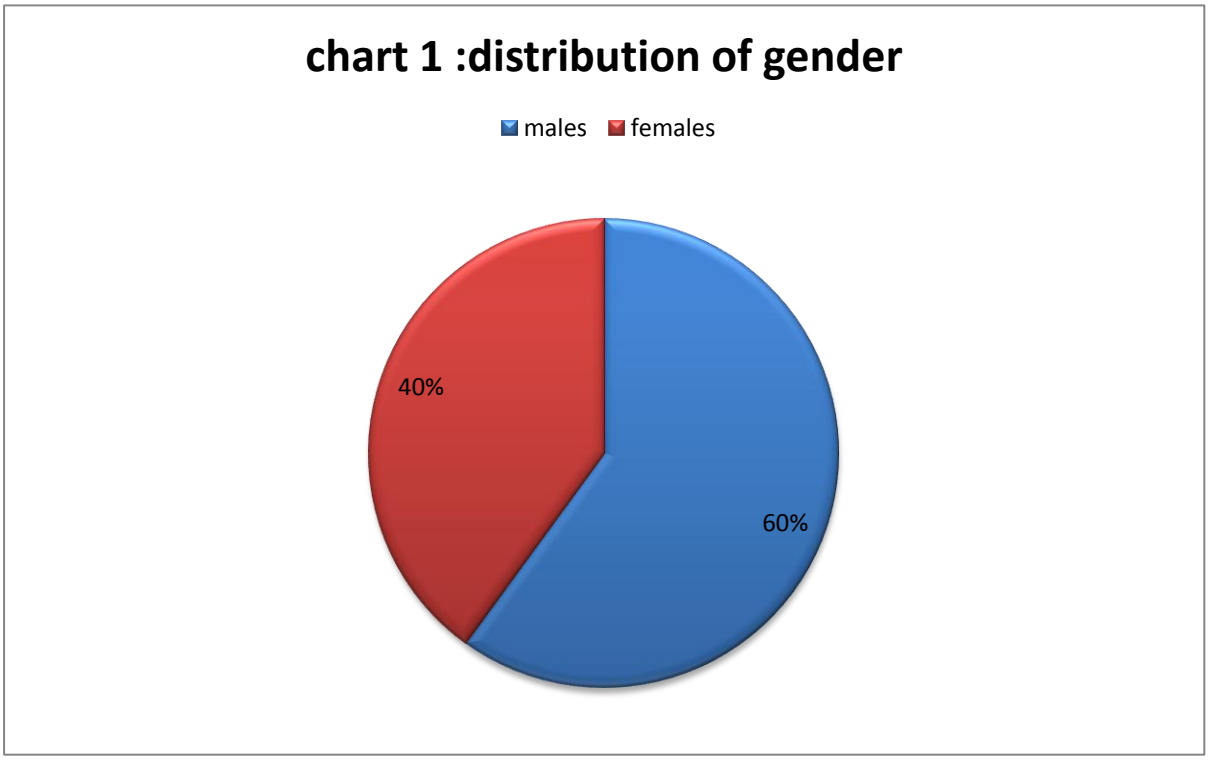


DESCRIPTIVE STATISTICS:

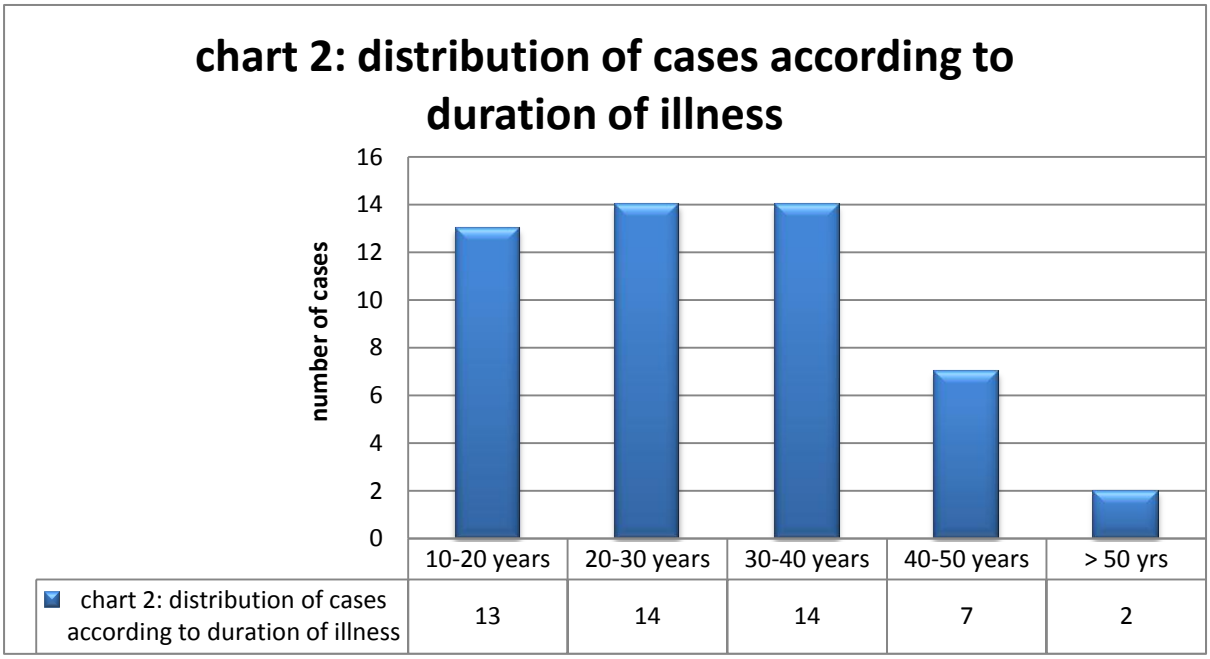
Of the total population who were involved in the study 30 were males (60%) and 20 were females (20%)

TABLE 6: GENDER WISE DISTRIBUTION OF POPULATION

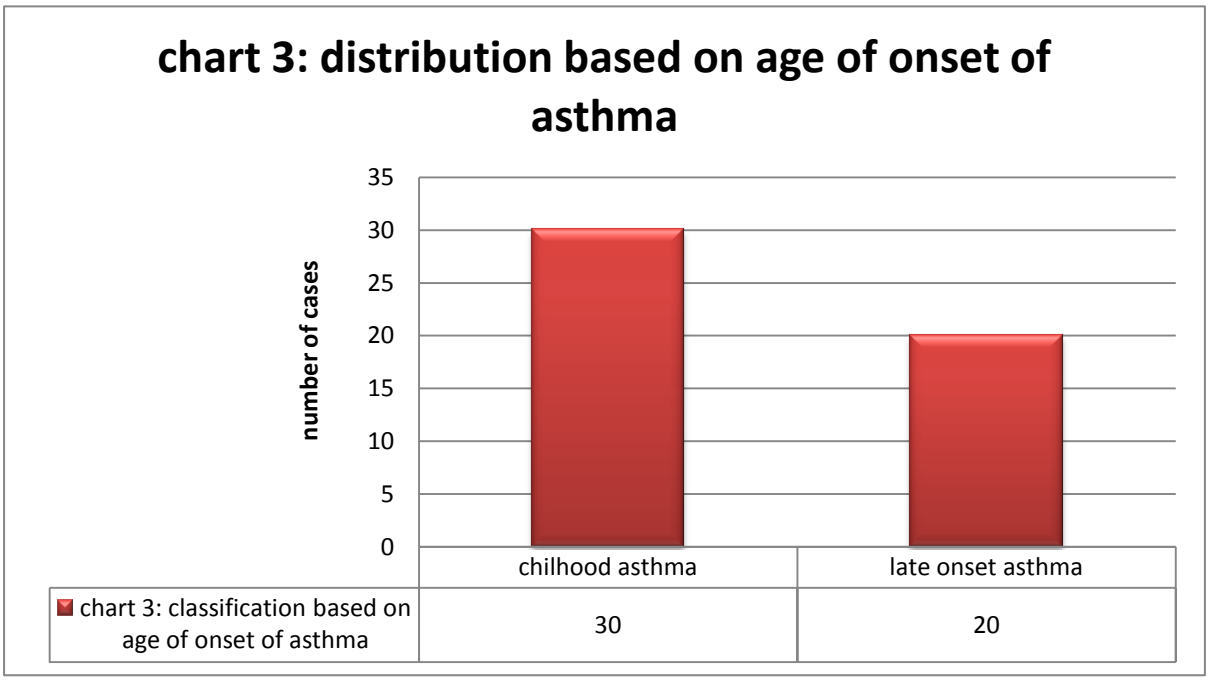
		Frequency	Percent
Valid	Male	30	60.0
	Female	20	40.0
	Total	50	100.0



The study population was distributed into 5 groups according to the duration of asthma symptoms. There were 13 people in the study had duration of 10-20 years (26%), 14 people had a duration of 20-30 years (28%), 14 people had a duration of 30-40 years (28%), 7 people had a duration of 40-50 years (14%) and 2 people had a duration > 50 years.



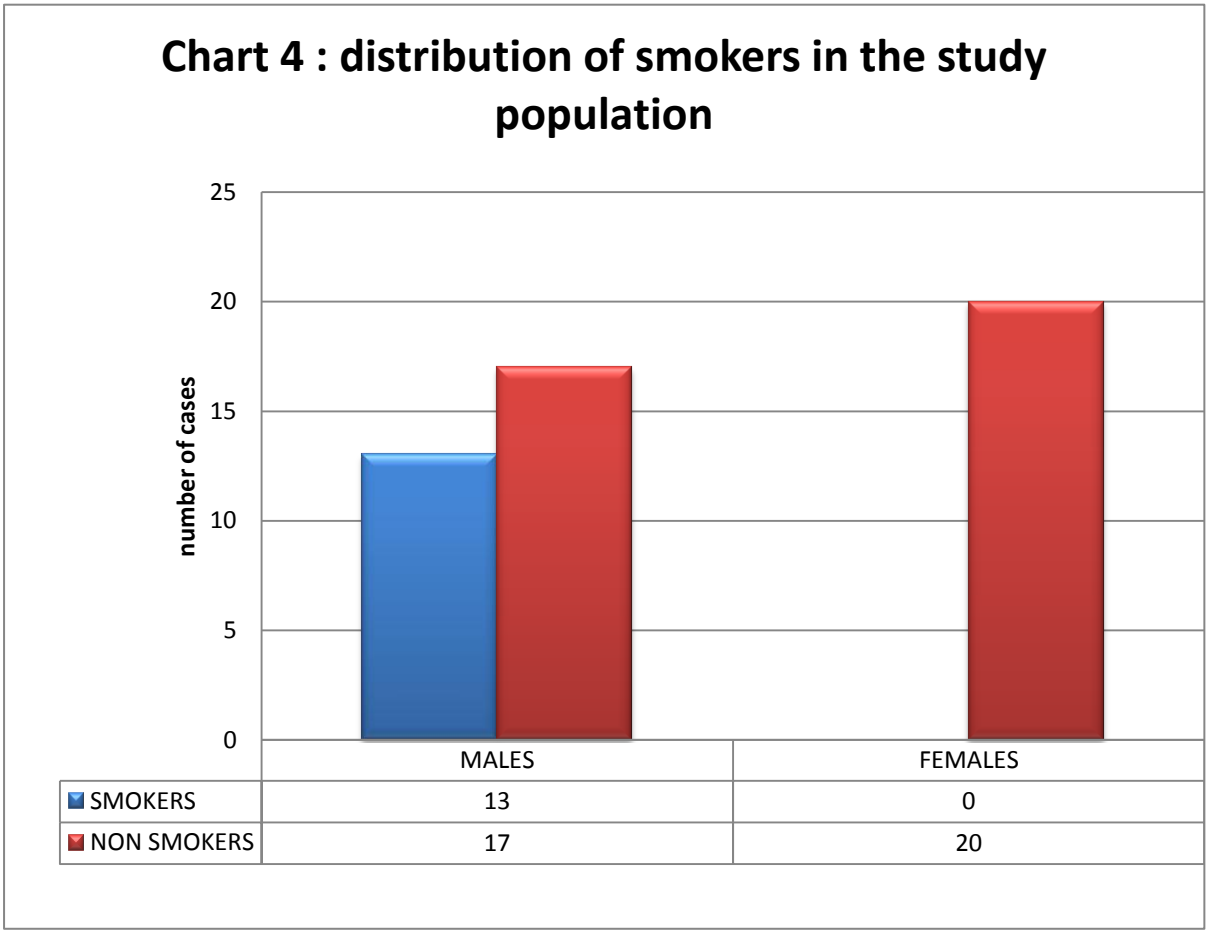
The population under study was classified into two groups. The first group with childhood onset of symptoms. This group had 30 patients. The other group had patients with onset of symptoms after the age of 20 years. This group had 20 patients.



Amongst the study group there were 13 cases (26%) with smoking history. All the cases were males.

TABLE 7: SMOKERS

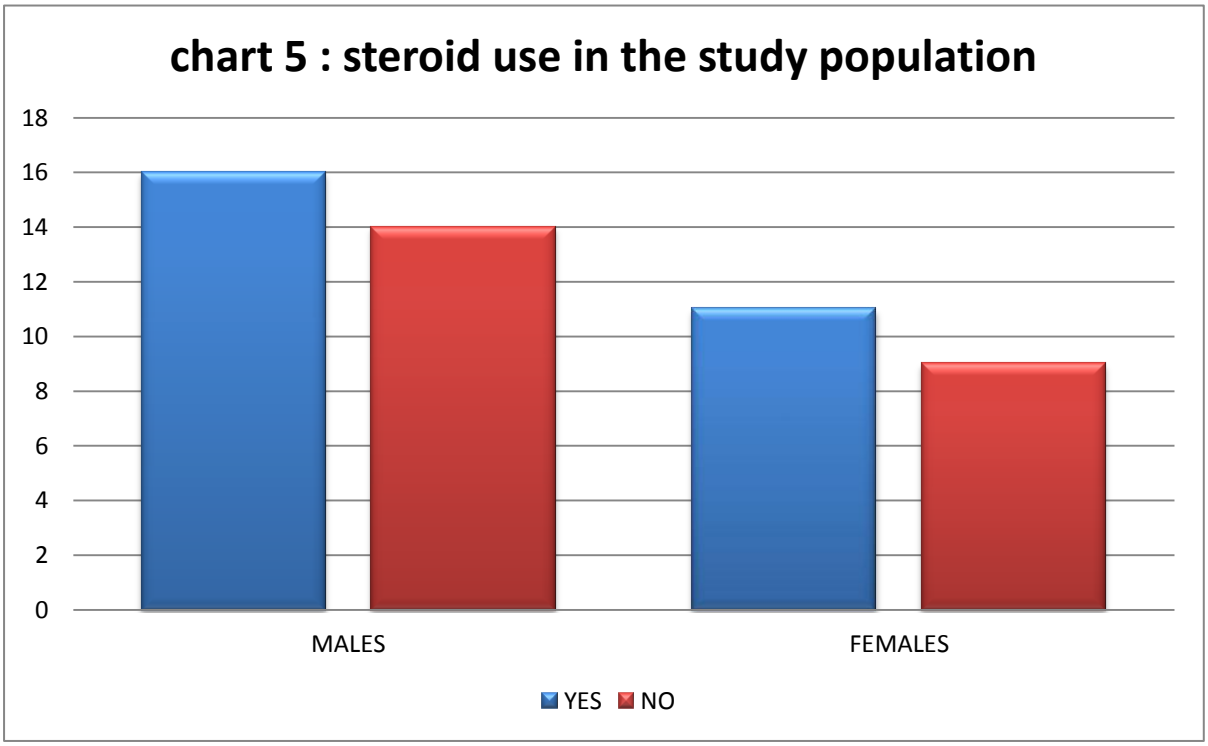
		Frequency	Percent
Valid	Yes	13	26.0
	No	37	74.0
	Total	50	100.0



Use of steroid in the population was studied along with other variables. 27 cases had a positive history of steroid use(both oral and inhaled form) which amounted to 54% of the study population and 23 cases had negative history for steroid use which amounted to 46% of the study population. 11 of them were females and 16 of them were males.

TABLE 8 :USE OF STEROID

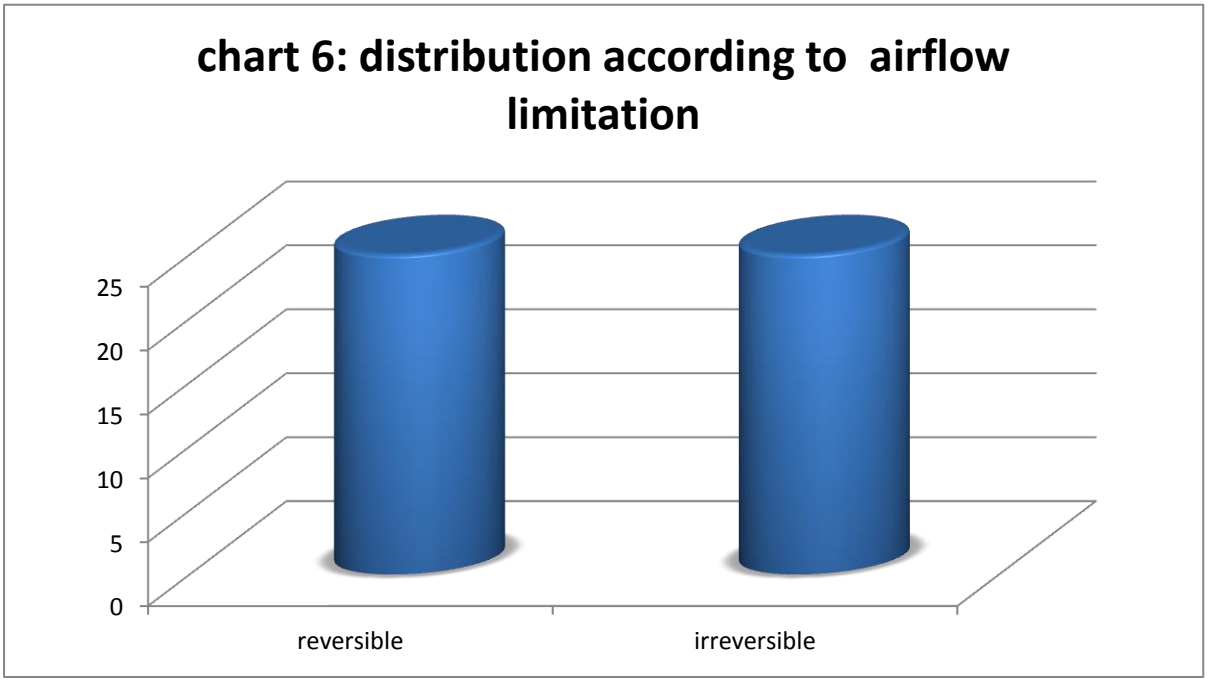
		Frequency	Percent
Valid	Yes	27	54.0
	No	23	46.0
	Total	50	100.0



Improvement in fev_1 >12% or 200ml in pulmonary function test following bronchodilator nebulisation and oral steroids-steroid trail (for those who did not show improvement after bronchodilator nebulisation) characterised the reversibility of airway obstruction. The population was categorised into two groups with this outcome. Cases with reversible airflow obstruction (25 patients) and those with irreversible airflow obstruction (25 patients).

TABLE 9: REVERSIBILITY OF AIRFLOW LIMITATION

		Frequency	Percent
Valid	Yes	25	50.0
	No	25	50.0
	Total	50	100.0

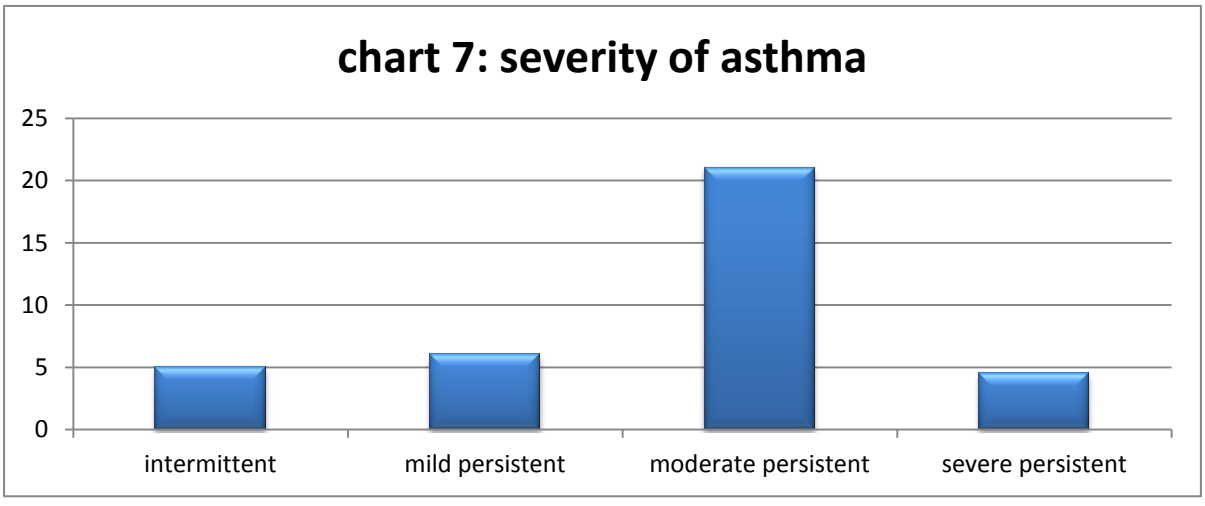


The above value suggested that 50% of the population under study who had bronchial asthma had irreversible air flow obstruction. Thus a high prevalence of irreversible airflow limitation was noted among asthmatics.

Asthma severity was classified according to the guidelines proposed by GINA. It was divided into 4 groups. 1) Intermittent 2) mild persistent 3) moderate persistent 4) severe persistent. There were 5,6, 21and 18 cases in intermittent, mild persistent, moderate persistent and severe persistent groups respectively.

TABLE 10:ASTHMA SEVERITY

		Frequency	Percent
Valid	Intermittent	5	10.0
	Mild	6	12.0
	Moderate	21	42.0
	Severe	18	36.0
	Total	50	100.0



RESULTS OF ANALYSIS:

With the above data a comparison was made between the variables and the reversibility of airflow limitation in the cases and an attempt made to bring out the correlation between those variables and the reversibility of airflow limitation. The variables considered were age of onset, duration of asthma, smoking history , steroid usage, number of exacerbations of symptoms/year and severity of asthma.

AGE OF ONSET :

A correlation between age at onset of asthma and air flow limitation was plotted. The results are as follows.

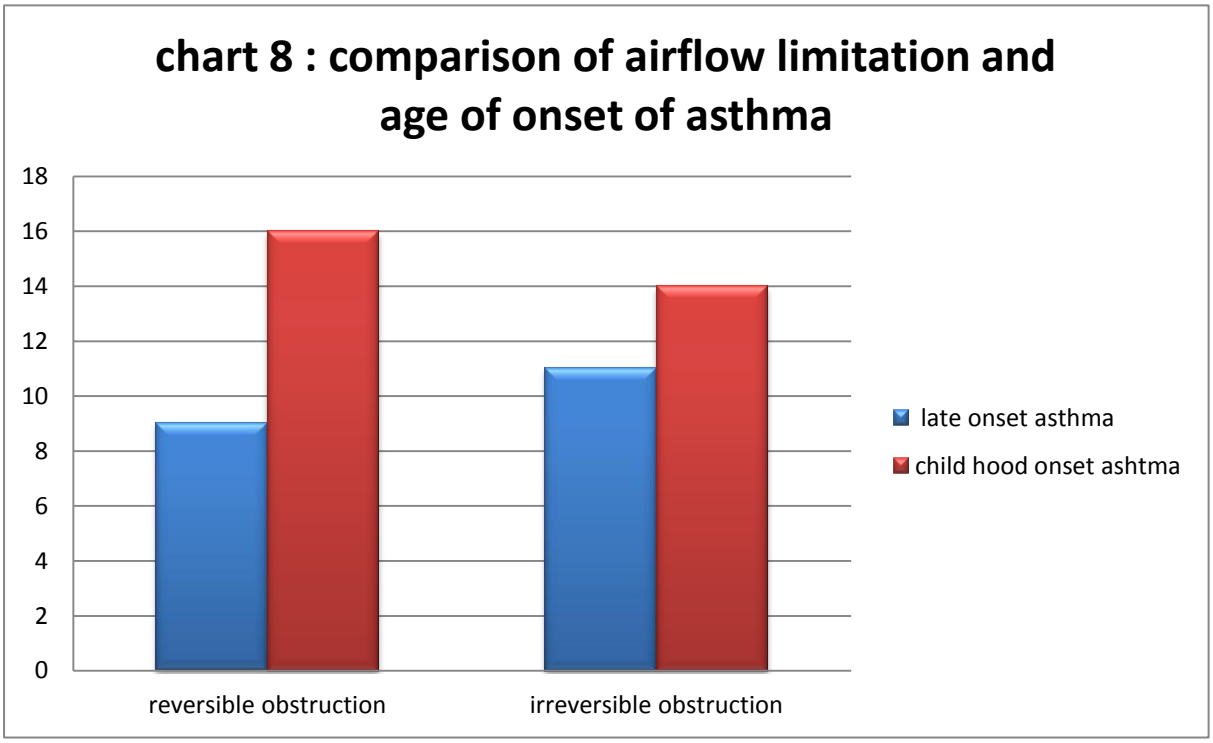
TABLE 11: age at onset of asthma and airflow limitation

			Age at Onset of Asthma		Total
			Late onset	Childhood	
Reversibility of Airflow Obstruction	Yes	Count	9	16	25
		% within Reversibility of Airflow Obstruction	36.0%	64.0%	100.0%
		% within Age at Onset of Asthma	45.0%	53.3%	50.0%
	No	Count	11	14	25
		% within Reversibility of Airflow Obstruction	44.0%	56.0%	100.0%
		% within Age at Onset of Asthma	55.0%	46.7%	50.0%
Total		Count	20	30	50
		% within Reversibility of Airflow Obstruction	40.0%	60.0%	100.0%
		% within Age at Onset of Asthma	100.0%	100.0%	100.0%

Chi-square tests

	Value	df	**Asymp. Sig.** (2-sided)
Pearson Chi-Square	.333(b)	1	.564
Continuity Correction(a)	.083	1	.773
Likelihood Ratio	.334	1	.563
Linear-by-Linear Association	.327	1	.568
No of Valid Cases	50		

A correlation between late onset asthma and irreversible airflow obstruction was sought. The values were statistically insignificant (p=.56(>.05)). But it was observed that the prevalence of irreversible airflow obstruction among the late onset asthma was greater (55%) than those with childhood onset asthma (46%).



DURATION OF ASTHMA:

An association between the duration of asthma and airflow obstruction was sought. The results are as follows.

TABLE 12: Duration of asthma and reversibility and airflow obstruction

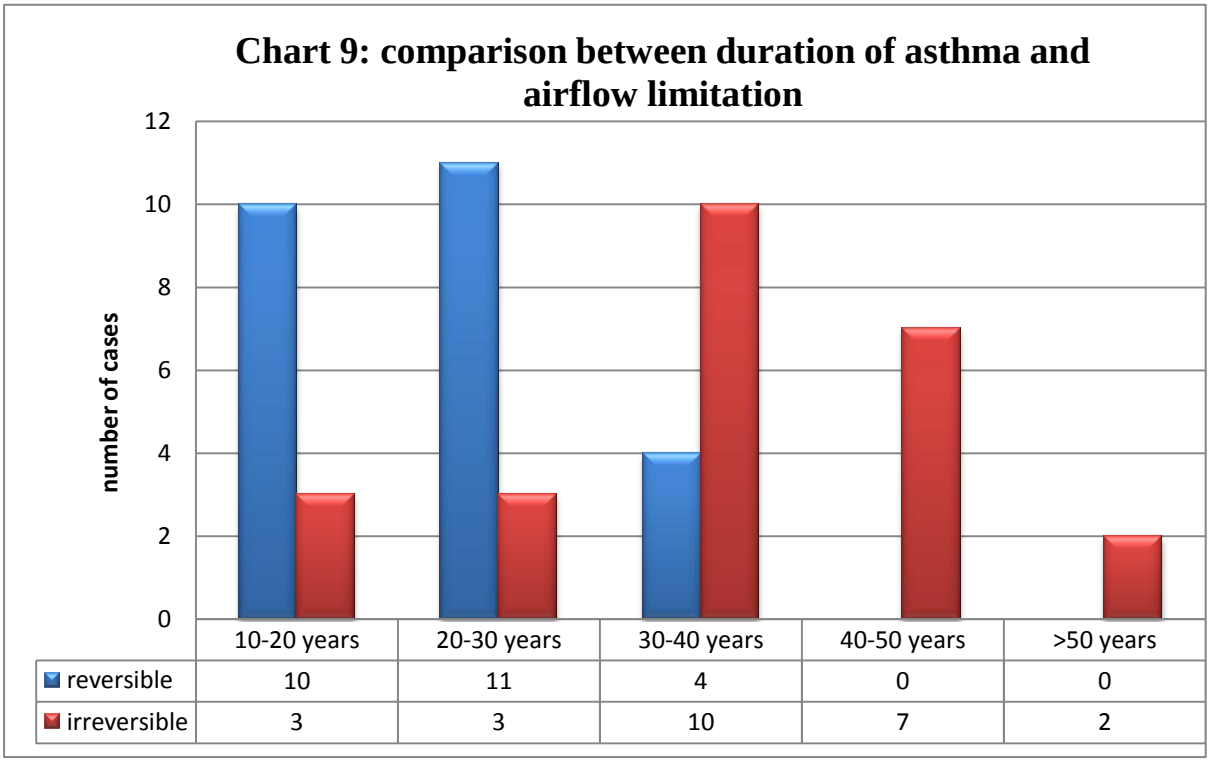
			Reversibility of Airflow Obstruction		Total
			Yes	No	
Duration of Asthma	Below 20	Count	10	3	13
		% within Duration of Asthma	76.9%	23.1%	100.0%
		% within Reversibility of Airflow Obstruction	40.0%	12.0%	26.0%
	20-30	Count	11	3	14
		% within Duration of Asthma	78.6%	21.4%	100.0%
		% within Reversibility of Airflow Obstruction	44.0%	12.0%	28.0%
	30-40	Count	4	10	14
		% within Duration of Asthma	28.6%	71.4%	100.0%

		% within Reversibility of Airflow Obstruction	16.0%	40.0%	28.0%
	40-50	Count	0	7	7
		% within Duration of Asthma	.0%	100.0%	100.0%
		% within Reversibility of Airflow Obstruction	.0%	28.0%	14.0%
	Above 50	Count	0	2	2
		% within Duration of Asthma	.0%	100.0%	100.0%
		% within Reversibility of Airflow Obstruction	.0%	8.0%	4.0%
Total		Count	25	25	50
		% within Duration of Asthma	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

Chi-square tests

	Value	Df	**Asymp. Sig.** (2-sided)
Pearson Chi-Square	19.912(a)	4	.001
Likelihood Ratio	23.970	4	.000
Linear-by-Linear Association	16.629	1	.000
N of Valid Cases	50		

There was a strong association established between the duration of asthma and the reversibility of airflow limitation. The patients with longer duration had irreversible airflow obstruction. This was statistically significant p value .001(highly significant).



There was a difference in the time period for the occurrence of irreversible airflow obstruction amongst the late onset and child hood onset asthma.

Those within late onset group had irreversible airflow limitation as early as 16 yrs (10-20 years interval) and those with childhood asthma had irreversible airflow limitation around 33years (30-40 years interval).

Smoking and use of steroid were seen as factors which were distributed throughout this distribution. Even though the data suggests that irreversible air flow obstruction is seen as early as 16 years the influence of steroids and smoking was seen in the groups 10-20 years and 20-30 years. Duration >30 years was undisputedly associated with irreversible airflow limitation irrespective of the smoking and steroid use in late onset asthma group. Similarly Duration >40 years was undisputedly associated with irreversible airflow limitation in the childhood onset asthma group. **Thus late onset asthma has been found to have a relatively earlier onset of irreversible obstruction than childhood onset asthma.**

Mean ages of the study population under the reversible airway obstruction and irreversible airway obstruction were 34 and 54 years respectively

TABLE 13 : Mean ages of study population

	Reversibility of Airflow Obstruction	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Yes	25	34.96	8.653	1.731
	No	25	53.64	9.945	1.989

SMOKING:

Smoking was prevalent only in the male gender in this study. An association between the reversibility of airflow obstruction and smoking was matched.

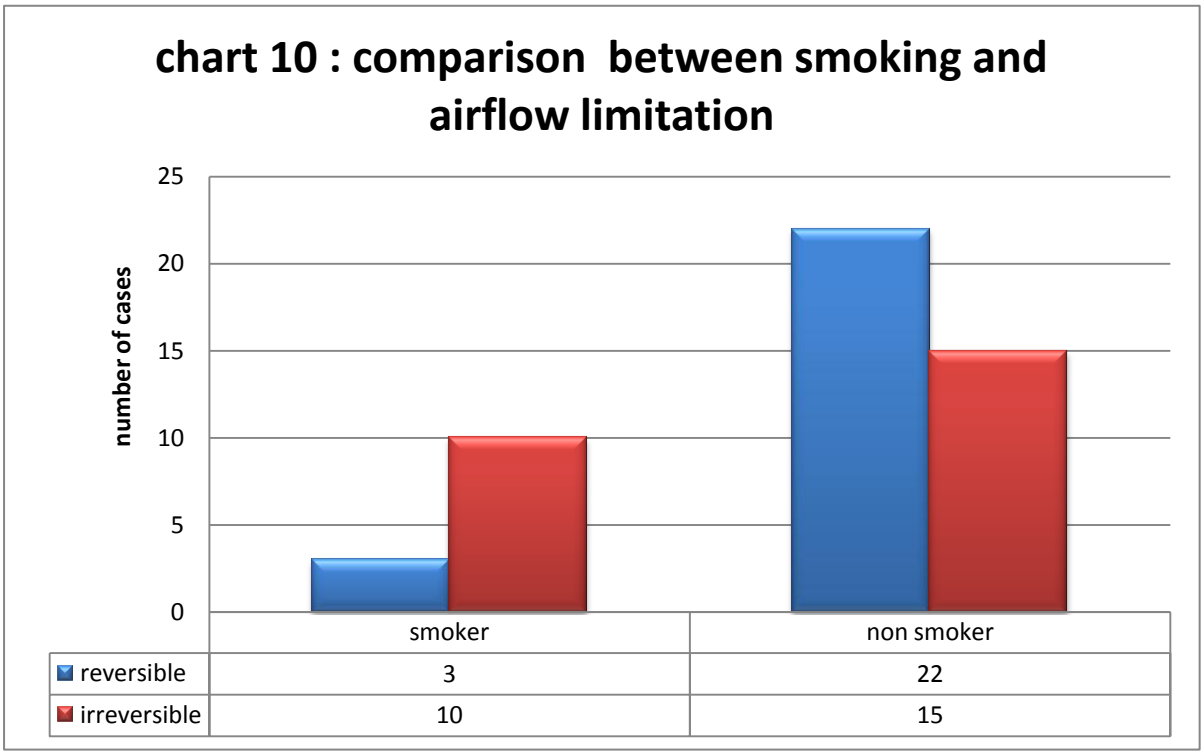
TABLE 14 : Smoking and reversibility of airflow obstruction

			Reversibility of Airflow Obstruction		Total
			Yes	No	
Smoker	Yes	Count	3	10	13
		% within Smoker	23.1%	76.9%	100.0%
		% within Reversibility of Airflow Obstruction	12.0%	40.0%	26.0%
	No	Count	22	15	37
		% within Smoker	59.5%	40.5%	100.0%
		% within Reversibility of Airflow Obstruction	88.0%	60.0%	74.0%
Total		Count	25	25	50
		% within Smoker	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

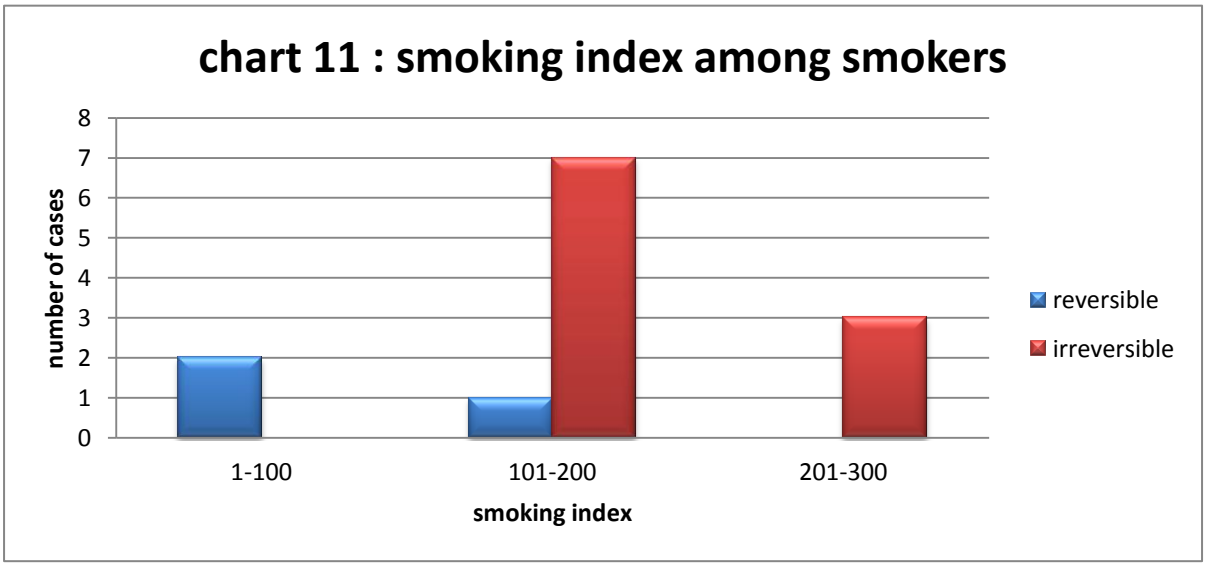
Chi-square tests

	Value	df	**Asymp. Sig.** (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.094(b)	1	.024		
Continuity Correction(a)	3.742	1	.053		
Likelihood Ratio	5.309	1	.021		
Fisher's Exact Test				.051	.025
Linear-by-Linear Association	4.992	1	.025		
N of Valid Cases	50				

The above statistical data shows that prevalence of smoking in cases with irreversible airflow limitation was higher among chronic asthmatics. The p value is statistically significant (.02).



Also a correlation was made between the smoking index and the reversibility of the airflow obstruction amongst the smokers. It was found that those with irreversible airflow obstruction had a smoking index more than 100.



USE OF CORTICOSTEROIDS:

The study also witnessed many cases with steroid usage. The steroid use among the people varied. Both inhalational and oral corticosteroids were included as steroid intake. A correlation between steroid usage and its protective effect over the reversibility of airflow limitation was observed. The results are as follows.

TABLE 15: steroid usage and irreversible airflow obstruction

			Reversibility of Airflow Obstruction		Total
			Yes	No	
Use of Steroid	Yes	Count	15	12	27
		% within Use of Steroid	55.6%	44.4%	100.0%
		% within Reversibility of Airflow Obstruction	60.0%	48.0%	54.0%
	No	Count	10	13	23
		% within Use of Steroid	43.5%	56.5%	100.0%
		% within Reversibility of Airflow Obstruction	40.0%	52.0%	46.0%
Total		Count	25	25	50
		% within Use of Steroid	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

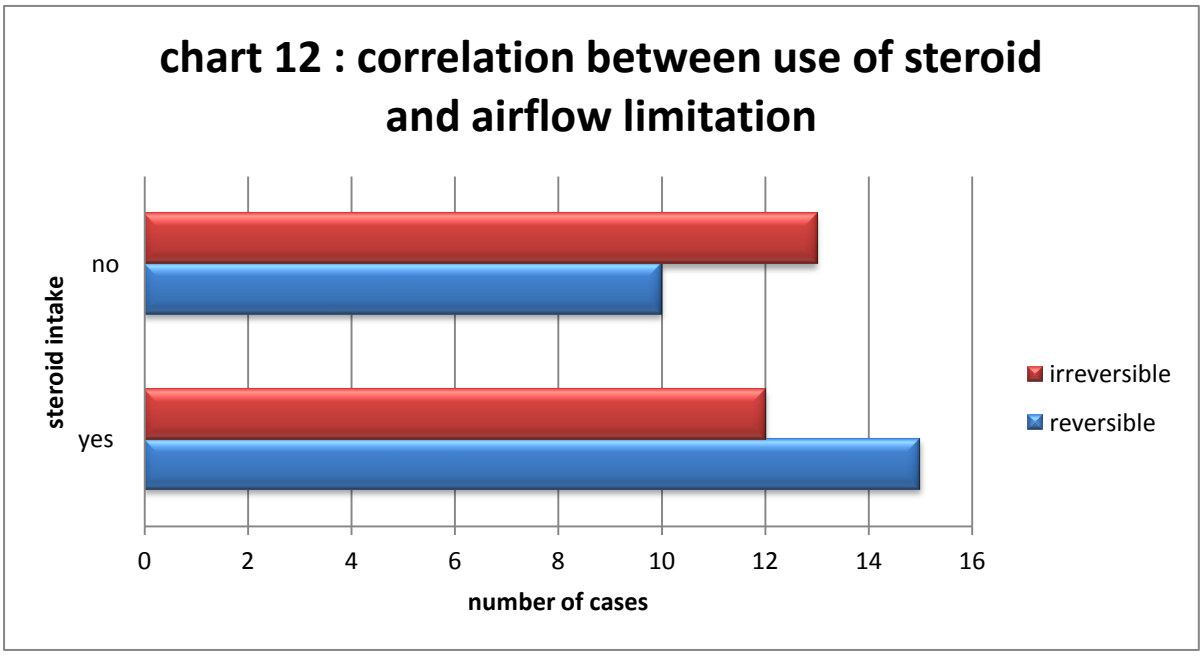
Chi-square tests

	Value	df	**Asymp. Sig.** (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.725(b)	1	.395		
Continuity Correction(a)	.322	1	.570		
Likelihood Ratio	.726	1	.394		
Fisher's Exact Test				.571	.285
N of Valid Cases	50				

It was observed that use of steroid was not statistically significant in prevention of irreversible airflow limitation in patients with asthma duration >10 years. The p value was .395(>.05)

Although certain facts were observed

- Amongst the male smokers with the asthma duration of 10-20 years in the late onset asthma group, (4 cases) one case was on steroid. 3 cases had irreversible airflow limitation and the case with steroid use had reversible airflow limitation.
- As observed previously late onset asthma had irreversible airflow limitation one decade ahead (20-30 years) of the childhood asthma where it was observed in 30-40 years of asthma duration. But both these groups also had reversible pattern demonstrated in the above specified range of asthma duration. This reversible pattern observation was made only in non smokers with steroid usage.



ASTHMA SEVERITY:

Asthma severity among the cases was plotted. An association between reversibility of airflow limitation and severity of asthma was sought.

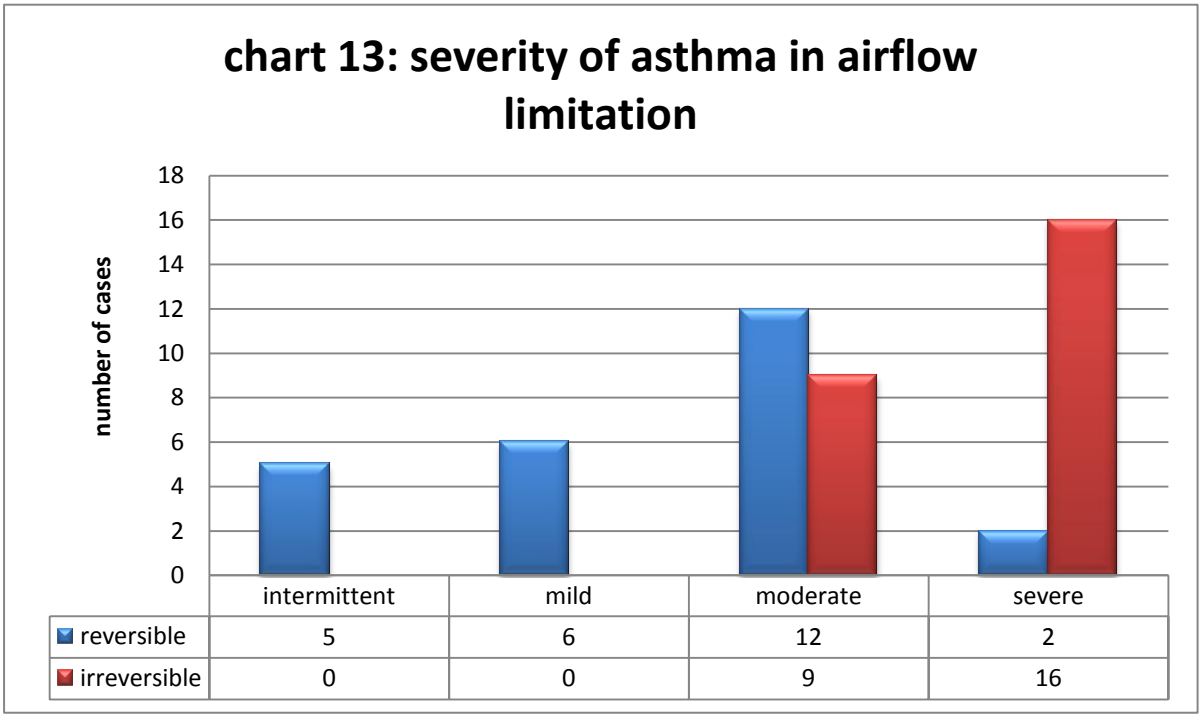
TABLE 16 : Asthma severity and reversibility of airflow obstruction

			Reversibility of Airflow Obstruction		Total
			Yes	No	
Asthma Severity	Intermittent	Count	5	0	5
		% within Asthma Severity	100.0%	.0%	100.0%
		% within Reversibility of Airflow Obstruction	20.0%	.0%	10.0%
	Mild	Count	6	0	6
		% within Asthma Severity	100.0%	.0%	100.0%
		% within Reversibility of Airflow Obstruction	24.0%	.0%	12.0%
	Moderate	Count	12	9	21
		% within Asthma Severity	57.1%	42.9%	100.0%
		% within Reversibility of Airflow Obstruction	48.0%	36.0%	42.0%
	Severe	Count	2	16	18
		% within Asthma Severity	11.1%	88.9%	100.0%
		% within Reversibility of Airflow Obstruction	8.0%	64.0%	36.0%
Total		Count	25	25	50
		% within Asthma Severity	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

Chi-square tests

	Value	df	**Asymp. Sig.** (2-sided)
Pearson Chi-Square	22.317(a)	3	.000
Likelihood Ratio	28.075	3	.000
Linear-by-Linear Association	20.082	1	.000
N of Valid Cases	50		

It was found that irreversible airflow limitation was seen prevalently in two groups-moderately persistent and severe persistent. Among this severely persistent asthma was found to be more associated with irreversible airflow limitation. Irreversible airflow limitation was significantly associated with severe persistent asthma. The p value was< .001(highly significant).



NUMBER OF EXACERBATIONS/YEAR:

An analysis was done to see the number of exacerbations/year in cases with the both reversible and irreversible airflow limitation and the results were tabulated.

TABLE 17 : Number of exacerbations in asthmatics

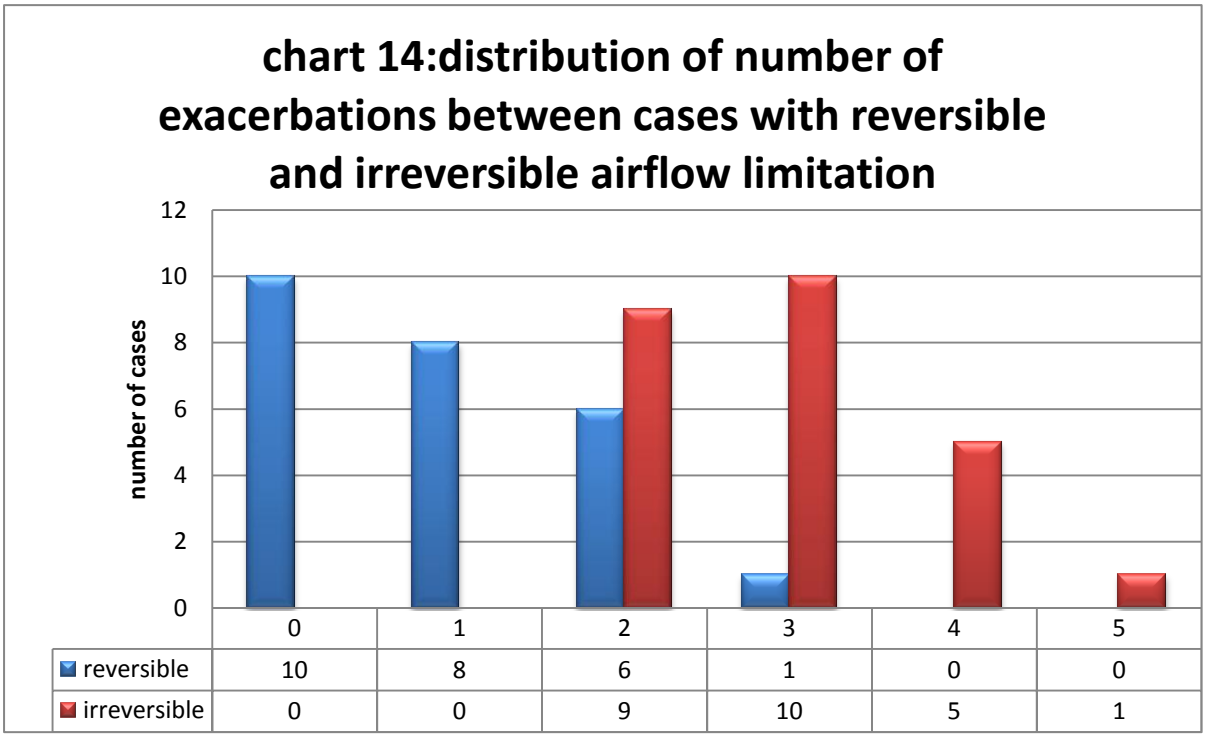
			Reversibility of Airflow Obstruction		
			Yes	No	Total
No. of Exacerbations per year	0	Count	10	0	10
		% within No. of Exacerbations per year	100.0%	.0%	100.0%
		% within Reversibility of Airflow Obstruction	40.0%	.0%	20.0%
	1	Count	8	0	8
		% within No. of Exacerbations per year	100.0%	.0%	100.0%
		% within Reversibility of Airflow Obstruction	32.0%	.0%	16.0%
	2	Count	6	9	15
		% within No. of Exacerbations per year	40.0%	60.0%	100.0%

		% within Reversibility of Airflow Obstruction	24.0%	36.0%	30.0%
	3	Count	1	10	11
		% within No. of Exacerbations per year	9.1%	90.9%	100.0%
		% within Reversibility of Airflow Obstruction	4.0%	40.0%	22.0%
	4	Count	0	5	5
		% within No. of Exacerbations per year	.0%	100.0%	100.0%
		% within Reversibility of Airflow Obstruction	.0%	20.0%	10.0%
	5	Count	0	1	1
		% within No. of Exacerbations per year	.0%	100.0%	100.0%
		% within Reversibility of Airflow Obstruction	.0%	4.0%	2.0%
Total		Count	25	25	50
		% within No. of Exacerbations per year	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

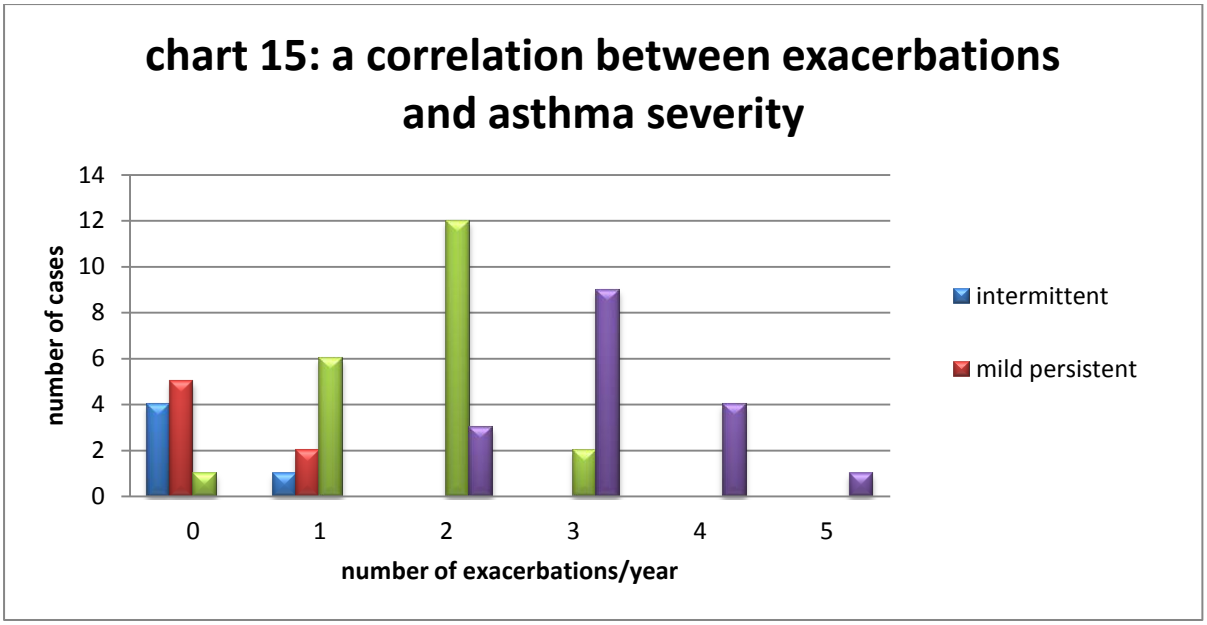
Chi-square tests

	Value	df	**Asymp. Sig**. (2-sided)
Pearson Chi-Square	31.964(a)	5	.000
Likelihood Ratio	42.422	5	.000
Linear-by-Linear Association	27.943	1	.000
N of Valid Cases	50		

It was found that cases with irreversible airflow limitation had increased number of exacerbations of the symptoms in a year. This was statistically significant –p value <.001.



Also along with this a graph was plotted comparing the number of exacerbation/year and the severity of the asthma in the cases.



PREVALENCE OF CHRONIC COUGH:

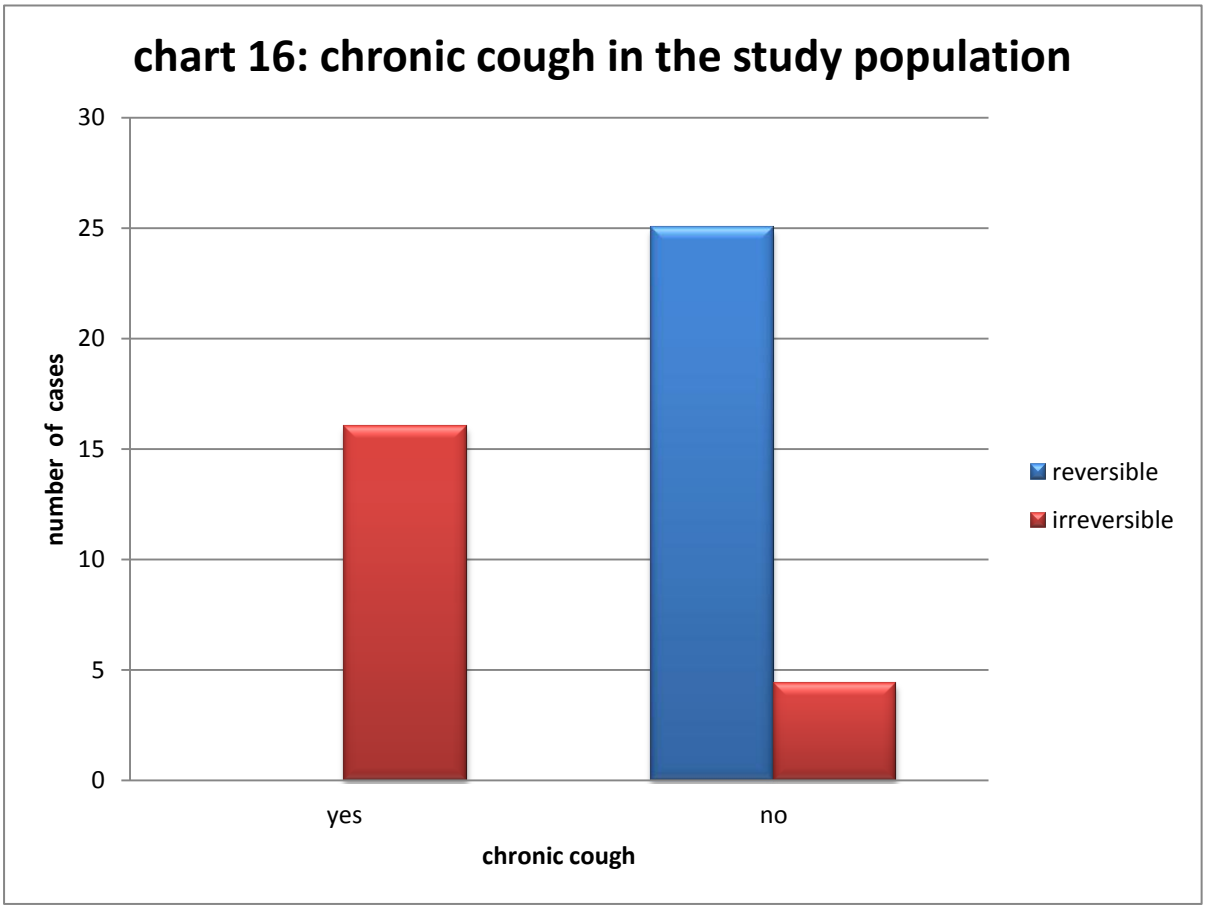
The study also saw that only irreversible airflow limitation was associated with symptoms of chronic bronchitis .The value was statistically significant p-<.001

TABLE 18: chronic cough among study population

			Reversibility of Airflow Obstruction		Total
			Yes	No	
Chronic Cough	Yes	Count	0	16	16
		% within Chronic Cough	.0%	100.0%	100.0%
		% within Reversibility of Airflow Obstruction	.0%	64.0%	32.0%
	No	Count	25	9	34
		% within Chronic Cough	73.5%	26.5%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	36.0%	68.0%
Total		Count	25	25	50
		% within Chronic Cough	50.0%	50.0%	100.0%
		% within Reversibility of Airflow Obstruction	100.0%	100.0%	100.0%

Chi-square tests

	Value	df	**Asymp. Sig.** (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	23.529(b)	1	.000		
Continuity Correction(a)	20.680	1	.000		
Likelihood Ratio	30.016	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	23.059	1	.000		
N of Valid Cases	50				



It was found that cases with irreversible airway obstruction with the longer duration had the symptom of chronic cough mimicking chronic bronchitis compared to those with lesser duration of the disease.

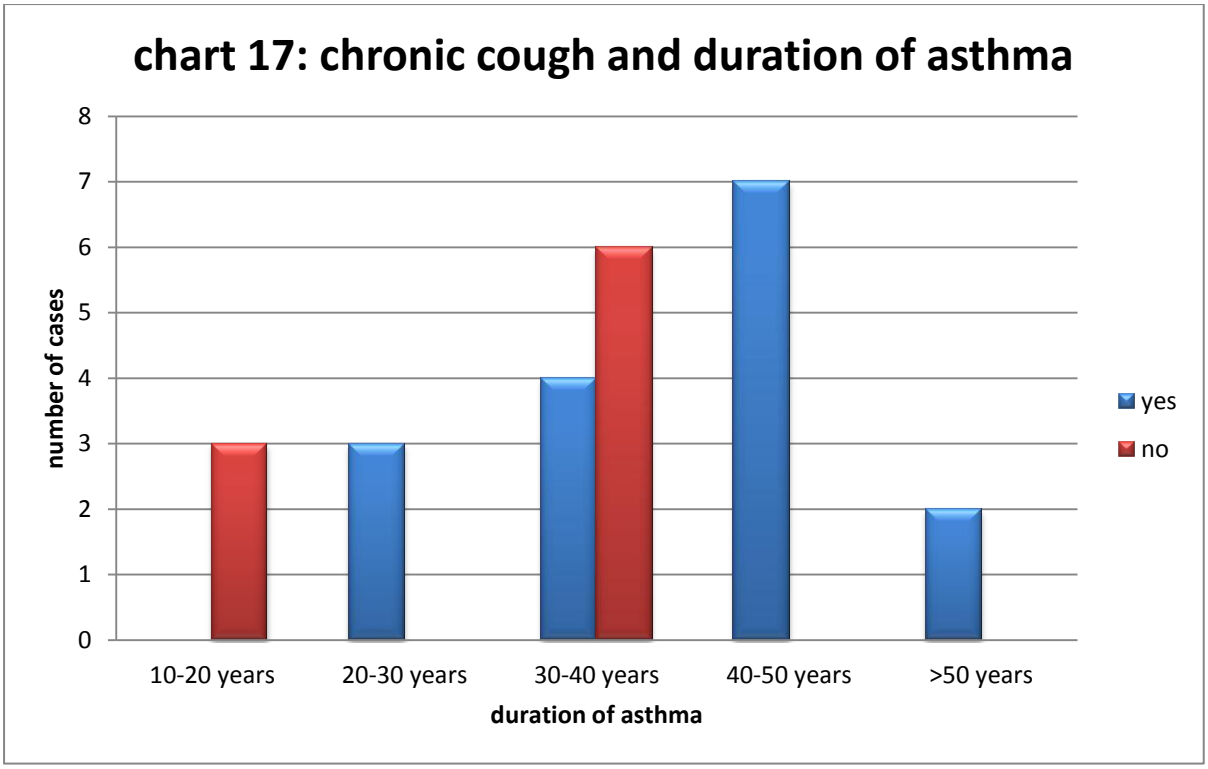
Reversibility of Airflow Obstruction				Chronic Cough		Total
				Yes	No	
Yes	Duration of Asthma	Below 20	Count		10	10
			% within Duration of Asthma		100.0%	100.0%
			% within Chronic Cough		40.0%	40.0%
		20-30	Count		11	11
			% within Duration of Asthma		100.0%	100.0%
			% within Chronic Cough		44.0%	44.0%
		30-40	Count		4	4
			% within Duration of Asthma		100.0%	100.0%
			% within Chronic Cough		16.0%	16.0%
	Total		Count		25	25
			% within Duration of Asthma		100.0%	100.0%
			% within Chronic Cough		100.0%	100.0%
No	Duration of Asthma	Below 20	Count	0	3	3
			% within Duration of Asthma	.0%	100.0%	100.0%
			% within Chronic Cough	.0%	33.3%	12.0%
		20-30	Count	3	0	3
			% within Duration of Asthma	100.0%	.0%	100.0%
			% within Chronic Cough	18.8%	.0%	12.0%
		30-40	Count	4	6	10
			% within Duration of Asthma	40.0%	60.0%	100.0%
			% within Chronic Cough	25.0%	66.7%	40.0%

		40-50	Count	7	0	7
			% within Duration of Asthma	100.0%	.0%	100.0%
			% within Chronic Cough	43.8%	.0%	28.0%
		Above 50	Count	2	0	2
			% within Duration of Asthma	100.0%	.0%	100.0%
			% within Chronic Cough	12.5%	.0%	8.0%
	Total		Count	16	9	25
			% within Duration of Asthma	64.0%	36.0%	100.0%
			% within Chronic Cough	100.0%	100.0%	100.0%

The data was statistically significant – p value .06. Therefore it is hypothesised that irreversible airflow obstruction with longer duration behaves clinically like a chronic obstructive lung disease. Chronic cough was defined as per the chronic bronchitis definition(>3months a year for two consecutive years).

Chi-square tests

Reversibility of Airflow Obstruction		Value	df	**Asymp. Sig.** (2-sided)
Yes	Pearson Chi-Square	.(a)		
	N of Valid Cases	25		
No	Pearson Chi-Square	14.583(b)	4	.006
	Likelihood Ratio	19.211	4	.001
	Linear-by-Linear Association	6.306	1	.012
	N of Valid Cases	25		



Irreversible air flow obstruction and its correlation

Statistically significant	**Statistically insignificant**
Duration of asthma	Age of onset of asthma
Smoking	Use of steroid
Asthma severity	
Number of exacerbations/year	
Chronic cough	

DISCUSSION

DISCUSSION

Years of medical school teaching and medical practice has believed Asthma to be a chronic inflammatory disease of the airways especially the medium sized bronchi that is characterised by variable and reversible airflow obstruction. But recently there are a lot of studies in the international forum that have challenged this view. Asthma has been seen as one of the forerunners of COPD, which is characterised by irreversibility of airflow obstruction. This study was conducted in the view to analyse the results of the newer studies which have shown irreversible airflow obstruction in asthmatics.

In our country a baseline Pulmonary Function Tests-PFT (using spirometer) was not practiced widespread in the past, when a case was first diagnosed as asthma. So this study has focussed much on patient's history as the major tool for confirming the diagnosis of asthma in them. PFT here was used as a tool only to demonstrate the reversibility of airflow obstruction. In the PFT, values that were considered for this study were FEV_1 (forced expiratory volume in first second),FVC(forced vital capacity or timed vital capacity), FEV_1/FVC.

In this study it was found that 50% of the study population had a irreversibility of airway obstruction. Most of them were from the male gender (68%) amongst which a considerable number of smokers were present (26%). A

gender wise significance could not be associated with the irreversibility of airway obstruction as the female gender in the study group lacked smokers which stood as a confounding factor.

Duration of asthma was found to be a single independent factor associated with the development of irreversible airflow obstruction in asthmatics in the study population. There are also supporting studies regarding this view. In a study published in the Eur Respir J 2004; 24: 122–128 by D. Bumbacea et al the parameters associated with the persistent airflow limitation in chronic severe asthma was analysed. It had proved that patients with severe form of the disease spectrum had a longer duration of the disease. The same study also suggested that use of steroid did not have any influence in the prevention of irreversibility in asthmatics. The similar results were obtained in our study with the use of steroid in the patients having an insignificant association with irreversible airflow obstruction in asthmatics. But the study found that those patients who had use of steroids still demonstrated reversibility of airflow limitation when compared to the cases that had similar duration of asthma. This sheds a view that although the use of steroid could not prevent the development of irreversible airflow obstruction it may prolong the duration of asthma with reversibility of the airflow limitation.

Prevalence of smoking among the irreversible airflow obstruction was high and statistically significant. This is although suggestive of additive effect to the asthma in the development of irreversible airflow

obstruction in asthmatics; it does not stand as an independent factor in the development of the irreversible airflow obstruction. Similar results were achieved in the study published by Alan .L. James et al in his study published in the American Journal of Respiratory and critical care medicine Vol 171 2005. The study also saw that among the late onset asthmatics with duration of asthma <20 years smoking was detrimental in causing an irreversible pattern. Thus this study views smoking to have an additive effect in the disease pathology and also suggests that smoking has been associated with earlier onset of irreversibility of airflow limitation in asthmatics especially the late onset asthmatics.

The study population had two main groups. Late onset asthma and childhood onset asthma. The association of late onset asthma with severity of asthma and the poor lung function in the asthmatics was demonstrated by Baptist AP et al in the study published J Asthma 2013 Oct;50(8):836-41. In this study the association of late onset asthma with the irreversible airflow obstruction was not statistically significant. But the prevalence of the irreversible pattern was more with (55%) with the late onset asthma than the childhood group (46%).

Asthma severity was found to have a strong correlation with the irreversible airflow obstruction. Severe persistent asthma was seen to be highly prevalent (64%) among the irreversible airflow obstruction. This significant association is in accordance with the natural course of the asthma. Asthma over

the years of progression leads to airway remodelling and thus leads to a decline of lung function and then leads to irreversible airflow obstruction. This decline in lung function manifests as severe persistent asthma. These patients had a longer duration of illness and thus a severe decline in the lung function. A similar consensus was reached in the study published in the Eur Respir J 2004; 24: 122–128 by D. Bumbacea et al. Thus this study is of opinion that asthmatics with the longer duration of asthma had severe asthma and greater decline in lung function with irreversible airflow obstruction.

Another parameter considered in the study was number of exacerbations/ year or the number of hospitalisations /year for the sudden increase in severity of symptoms. The number of exacerbations/year was >2 in the study population with irreversible airflow obstruction as compared to those reversible pattern. Again this is in accordance with the natural history of asthma. The more the exacerbations more is the airway inflammation and more in the airway remodelling and more chance of irreversible airflow limitation. evidence to this is supported by the study published Matsunaga et al in Respir Med. 2013 Mar;107(3):355-60.

Asthmatics with irreversible airflow obstruction satisfied the criteria of COPD in this study as per the PFT. A probe on the symptoms of these patients and a comparison of these patients with those with reversible airflow limitation was made. The patients with irreversible airflow obstruction saw a large proportion(64%) of patients with cough which was of productive nature and that

lasted for more than 3 months a year. This had a resemblance to chronic bronchitis. The cases in the reversible airflow limitation group did not satisfy this pattern of cough. Most of them if so had only a dry cough. This evidence also speaks in favour of asthma as a forerunner and independent risk factor for the development of COPD. A similar result was obtained in the study published by J M Vonk et al in his study published in the Thorax 2003;58:322–327.

LIMITATIONS OF THE STUDY

1. This study was done in a small number of patients. Study in a larger population is needed.
2. A previous Pulmonary Function Test showing reversible airflow obstruction suggestive of asthma was not available with the participants who were enrolled as asthmatics in this study.
3. The study concentrated history from the patient as a major source of the data and a considerable population was elderly. Therefore more of subjective than of objective data was used.

CONCLUSION

CONCLUSION

Duration of asthma and asthma severity were independently associated with the development of irreversible airflow obstruction in asthmatics of >10 years duration. Smoking and lack of steroid played additive roles along with duration of asthma in the development of irreversible airflow obstruction. Age at onset did not find any significance in this study but further studied with larger population could bring out this association. With the development of irreversible obstruction these asthmatics behaved more like patients with COPD clinically (although pathological evidence was not done to confirm this) and thus it is evident that asthma is a indepent risk factor for COPD in a longer duration of course. This study helps us to recognise the risk factors associated with the acceleration of the disease process in asthmatics and thus helps us to take necessary steps like avoiding smoking, using inhaled corticosteroids for a better patient living. Also the study highlights the importance of Pulmonary Function Testing in monitoring the disease process. Finally the recognition of irreversibility of the airflow limitation is of immense importance for the management of these patients both in emergency rooms and in the daily practice schedules, failing this, leads to deleterious effect on the patient iatrogenically.

DISCLOSURE

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APPENDIX

PROFORMA

PATIENT INFORMATION SHEET

ASTHMA QUESTIONNAIRE

NAME: **AGE:** **SEX:** **OCCUPATION:**

Age of onset of symptoms:

Breathlessness- i) duration

ii) MMRC grading

iii) relation of episodes- a)day time

b)night time

iv) no.of. episodes requiring hospitalisation for the past 1 year

v) seasonal variation

vi) early morning aggravation of symptoms

Cough –i) duration

ii) Nocturnal

iii) Seasonal variation

iv) dry or productive

v) Sputum

vi) recent change in sputum consistency?

Does strenuous activity brings out the symptom or aggravates it?

Has nebulisation achieved complete recovery of symptoms in the past?

Frequency of nebulisation

Able to perform activities without limitation in between symptoms?

h/o nasal polyps

h/o aspirin intolerance

h/o allergy

family h/o asthma

h/o tremors/palpitation

h/o bone pain/fracture

h/o oral thrush

PRESENT MEDICATIONS:

PERSONAL HABITS:

COMORBID ILLNESS:

GENERAL EXAMINATION

Pallor: **Icterus:** **Cyanosis:**

Clubbing : **Lymphadenopathy:** **JVP:**

Pulse rate: **Blood pressure:** **SPO2:**

CVS: **P/A:** **CNS:**

RS:

INVESTIGATION

1. CBC with ESR

2. Chest X-ray

3. ECG

4. Sputum for AFB & gram stain

5. Pulmonary function test

	Baseline value	After salbutamol nebulization	After 2 weeks oral prednisolone
FEV_1			
FVC			
FEV_1/FVC			

ASTHMA SEVERITY:

IMPRESSION:

SIGNATURE OF INVESTIGATOR SIGNATURE OF GUIDE

PATIENT CONSENT FORM

STUDY DETAIL :

STUDY CENTRE :

PATIENT'S NAME :

PATIENT'S AGE :

IDENTIFICATION NUMBER :

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However I understand that my identity would not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests.

Signature/thumb impression:

MASTERCHART

S.NO	NAME	AGE	SEX	OCCUPATION	AGE AT ONSET OF ASTHMA	DURATION OF ASTHMA	REVERSIBILITY OF AIRFLOW OBSTRUCYION	SMOKER	SMOKING INDEX	USE OF STEROID	NO.OF EXACERBATIONS/YEAR	ASTHMA SEVERITY	CHRONIC COUGH
1	raziya bee	52	2	house wife	1	2	0	0	0	0	3	3	1
2	lakshmi	46	2	house wife	1	2	1	0	0	1	2	3	0
3	vimalammal	64	2	house wife	1	3	0	0	0	1	4	4	1
4	kurshid begum	59	2	house wife	1	3	0	0	0	1	4	4	1
5	rani	34	2	vendor	1	1	1	0	0	0	0	1	0
6	kamala	36	2	maid	1	1	1	0	0	0	0	1	0
7	fathima	38	2	house wife	1	1	1	0	0	1	0	2	0
8	elumalai	35	1	plumber	1	1	0	1	2	0	2	3	0
9	imanullah	56	1	buisenes s	1	2	0	0	0	1	4	4	1
10	david	44	1	sanitary worker	1	2	0	1	2	0	3	4	1
11	selvaraj	50	1	coolie	1	2	1	0	0	1	3	4	0
12	mani	38	1	barber	1	1	0	1	2	0	3	4	0
13	mohammed	33	1	rice shop worker	1	1	1	0	0	0	0	3	0
14	ravi	42	1	auto driver	1	1	1	1	1	1	0	2	0
15	raja	37	1	coolie	1	1	0	1	2	0	2	3	0
16	chittibabu	46	1	coolie	1	2	1	0	0	1	2	3	0
17	jaffer	36	1	buisenes s	1	1	1	0	0	1	0	2	0
18	kandasamy	64	1	watchman	1	3	0	1	3	1	2	3	1
19	kesavan	72	1	teacher	1	4	0	1	2	1	5	4	1
20	sivalingam	68	1	watchman	1	3	0	0	0	1	3	3	1
2	pushpa	22	2	student	2	1	1	0	0	1	1	1	0

1												
22	shanti	19	2	student	2	1	1	0	0	0	0	2	0
23	mary	28	2	shop assistant	2	2	1	0	0	1	0	2	0
24	radha	32	2	vendor	2	2	1	0	0	0	2	3	0
25	zuleika bee	30	2	house wife	2	2	1	0	0	0	2	3	0
26	eashwari	38	2	shop assistant	2	3	1	0	0	1	2	3	0
27	ismath	42	2	house wife	2	3	1	0	0	1	1	3	0
28	radhika	44	2	maid	2	3	0	0	0	0	3	4	0
29	sivagami	46	2	house wife	2	3	0	0	0	0	2	4	0
30	parvathy	52	2	house wife	2	4	0	0	0	1	2	3	1
31	rajarajeshwari	56	2	house wife	2	4	0	0	0	1	2	4	1
32	rahamath nisha	60	2	house wife	2	4	0	0	0	0	3	4	1
33	annie	64	2	house wife	2	5	0	0	0	1	2	3	1
34	raju	19	1	student	2	1	1	0	0	1	0	1	0
35	karthick	22	1	BPO	2	1	1	0	0	0	1	3	0
36	arokya raj	28	1	coolie	2	2	1	0	0	1	0	1	0
37	humayun	32	1	mason	2	2	1	0	0	0	1	3	0
38	saamy	34	1	buisenes s	2	2	1	0	0	1	1	2	0
39	sivakumar	38	1	clerk	2	2	1	1	1	0	1	3	0
40	arunachalam	40	1	electrician	2	2	1	1	2	0	2	4	0
41	sahul hameed	44	1	buisenes s	2	3	1	0	0	1	1	3	0
42	chandran	45	1	coolie	2	3	1	0	0	1	1	3	0
43	duraisamy	47	1	auto driver	2	3	0	0	0	0	2	3	0
44	antony	48	1	fisherman	2	3	0	0	0	0	2	3	0
4	ganesan	48	1	coolie	2	3	0	1	2	0	3	4	0

45													
46	hariharan	50	1	vendor	2	3	0	1	3	0	3	4	0
47	jagannathan	54	1	watchman	2	4	0	0	0	1	3	4	1
48	ismail	58	1	buisenes s	2	4	0	0	0	1	3	4	1
49	syed	60	1	buisenes s	2	4	0	1	2	0	4	4	1
50	logannathan	65	1	watchman	2	5	0	1	3	1	4	4	1

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.2318/ME-1/Ethics/2012 Dt:04.04.2013
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on prevalence of irreversible airflow obstruction among chronic asthmatics in Govt. Royapettah Hospital" – For Project Work submitted by Dr.K.Venkatraman, MD (GM), PG Student, Govt. Royapettah Hospital, Chennai-14.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
29 MAY 2013
Kilpauk, Chennai-10.

29/5/13.
CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai