# A STUDY ON CORRELATION OF SERUM IMMUNOGLOBULIN E LEVELS AND ABSOLUTE EOSINOPHIL COUNT WITH SEVERITY OF BRONCHIAL ASTHMA AS ASSESSED BY LUNG SPIROMETRY

**Dissertation submitted in**

**Partial fulfillment of regulation for the award of**

**M.D. GENERAL MEDICINE**

**( BRANCH I )**

**The Tamilnadu DR.M.G.R. Medical University**

**Chennai , April 2015**

# CERTIFICATE

This is to certify that this bonafide dissertation in "CORRELATION OF SERUM IMMUNOGLOBULIN E LEVELS AND ABSOLUTE EOSINOPHIL COUNTS IN ASSESSING SEVERITY OF BRONCHIAL ASTHMA AS ASSESSED BY LUNG SPIROMETRY" done by **Dr. Priya Sreeraj,** under my guidance during the academic year 2012 to 2015.

This dissertation is submitted in partial fulfillment of the requirements for the award of Degree of **M.D degree in General Medicine**, **Branch I** by **The Tamilnadu Dr. M.G.R. Medical University, Chennai- 600 032.**

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# DECLARATION

I solemnly declare that this dissertation entitled "CORRELATION OF SERUM IMMUNOGLOBULIN E LEVELS AND ABSOLUTE EOSINOPHIL COUNTS IN ASSESSING SEVERITY OF BRONCHIAL ASTHMA AS ASSESSED BY LUNG SPIROMETRY " was done by me at Coimbatore Medical College and Government Hospital during the academic year 2012-2015 under the guidance and supervision of **Prof. Dr. Isaac Christian Moses M.D.**

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, towards the partial fulfilment of requirement for the award of M.D. Degree in General Medicine (Branch – I)

Place : Coimbatore

Date : **Dr. PRIYA SREERAJ**

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Finally, I wholeheartedly thank **ALL MY PATIENTS,** who formed the backbone of this study without which this would not have become a reality.

# CONTENTS

# ABBREVIATIONS

| | | |
|---|---|---|
| AI | - | Airway Inflammation |
| AEC | - | Absolute Eosinophil count |
| AR | - | Allergic Rhinitis |
| AHR | - | Air way Hyper Responsiveness |
| APC | - | Antigen Presenting Cells |
| BDR | - | Broncho dilatator Response |
| BTS | - | British Thoracic Society |
| CD4 | - | Cluster of differentiation. |
| DC | - | Differential Count |
| FEV1 | - | Forced Expiratory Volume in 1 sec |
| FVC | - | Forced vital capacity |
| ECP | - | Eosinophilic Cationic Protein |
| EPO | - | Eosinophil Peroxidase |
| GINA | - | Global Initiative for Asthma |
| H & E | - | Haematoxylin & Eosin |
| HPE | - | High Power field |
| IL | - | Interleukins |
| ICS | - | Inhaled corticosteroids |
| IU/ml | - | International units/millilitre |
| Ig E | - | Immunoglobulin E |

| | | |
|---|---|---|
| LT | - | Leukotriene |
| LABA | - | Long acting beta agonist |
| MBP | - | Major Basic Protein |
| NSE | - | Nasal Smear Eosinophilis |
| NSC | - | Nasal Smear Cytology |
| OCS | - | Oral corticosteroid |
| PEF | - | Peak Expiratory Flow |
| PFT | - | Pulmonary Function Tests |
| PGD2, PGF2 | - | Prostaglandins |
| RAST | - | Radio Allergysorbent test |
| RCT | - | Randomized Control Studies |
| SSE | - | Sputum Smear Eosinophilis |
| SSC | - | Sputum Smear Cytology |
| SR | - | Sustained Release |

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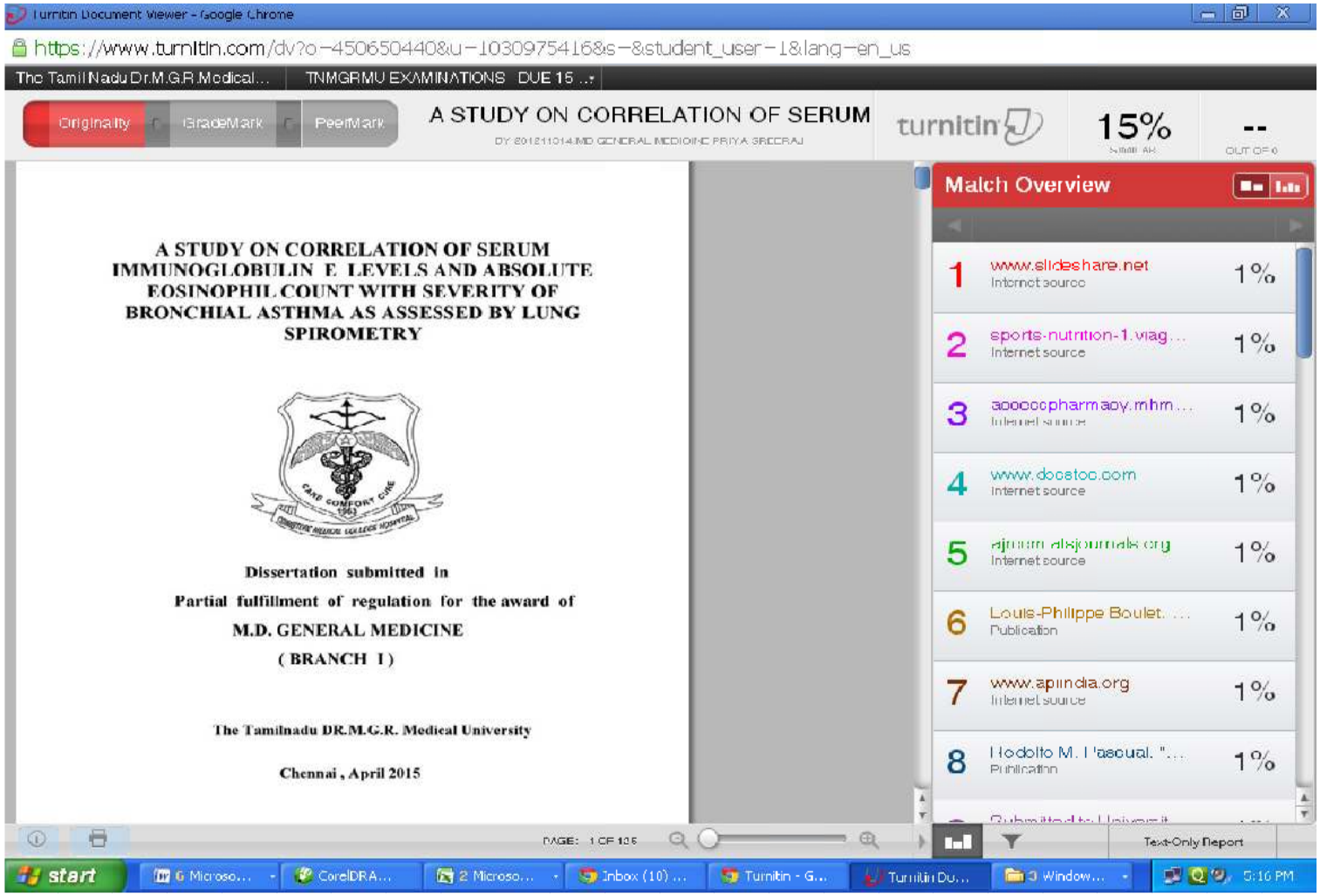
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# ABSTRACT


## BACKGROUND

In our country,there is a huge burden due to asthma and a huge proportion of these cases are left underrecognised,underestimated and undertreated.Asthma is now considered a single airway disease and hence comprehensive diagnosis,treatment and follow up is essential.Majority of asthma patienys are atopic according to population studies.The prevalence of asthma increases with increasing severity of asthma according to population studies.In asthma patients eosinophils are present in blood,sputum,bronchiallavage.Further studies are required to prove its association with severity of asthma

## AIMS AND OBJECTIVES

1. To establish an association between airway inflammation as assessed by absolute eosinophil count and disease severity.
2. To establish an association between atopy as demonstrated by serum Immunoglobulin E levels and disease severity.
3. To correlate the clinical presentation, Serum IgE and absolute eosinophil count with severity of bronchial asthma as assessed by lung spirometry.
4. To predict the prognosis and treatment outcome of bronchial asthma patients from absolute eosinophil count and serum Ig E levels.

## Methodology

100 patients who were diagnosed to have bronchial asthma in Coimbatore Medical College hospital were included in the study population. Risk factors, family history and other associated comorbid conditions were recorded .Severity was assessed by doing lung spirometry in all patients.Serum immunoglobulin E and absolute eosinophil count was done in patients for those classified into mild, moderate and severe groups.Correlation was assessed between each of these variables and severity.

## Results

Positive correlation was found between asthma severity and absolute eosinophil count in the severe persistent asthma group which was statistically significant.SerumIgE levels correlate with asthma severity and the mean Ig E in mild was 271.50 IU/mL,moderate group was 916.48 IU/mL and severe group was 1662.59 IU/mL.

## Conclusion

Serum immunoglobulin E and absolute eosinophil counts were found to have positive correlation with asthma severity. Estimation of these parameters can be used as simple tools in assessing asthma severity based on clinical grading.

Key words-Bronchial asthma,Absolute Eosinophil Count,Serum immunoglobulin E

# INTRODUCTION

Over the last few years, an increase in prevalence of allergic diseases like asthma and allergic rhinitis is seen. Both are common chronic diseases that affect the quality of life of patients and have a significant economic impact. About 300 million people worldwide suffer from asthma and this figure is projected to rise to 400 million by year 2025.

Nearly 5 Lakh people are hospitalised a year and nearly 250000 deaths occur due to the disease. Around 35% is the prevalence of allergic rhinitis in Europe and Australia . It shows a significant impact on people day to day life and if untreated it can lead to many symptoms.

In our country, there is a huge burden due to asthma though further data is required for finding out prevalence. Asthma Epidemiology Study Group of Indian Council of Medical Research found the prevalence of bronchial asthma in Indian adults as 2.38 %.

Today, our country's census is above 1 billion . This exploding of census itself suggests a huge increase of allergic diseases in our country which are left under recognised, underestimated and under treated in India.

Presently, bronchodilators and anti-inflammatory drugs are providing relief in majority of patients, though they do not produce

symptomatic relief to all patients. Despite the various treatment options available those in mild to severe group continue to have excacerbations with inhaled therapies, leading to large number of hospitalisations and visit to physicians

As there exists many asthma mimics, diagnosis of asthma needs supporting evidences like family history, history of allergy etc. Asthma now considered as single airway disease and hence comprehensive diagnosis, treatment and follow up of upper and lower respiratory tract is essential.

It has been observed in many studies that serum Ig E level is elevated in asthmatic and tracks with the severity of asthma. Eosinophil infiltration is hallmark feature of pathogenesis of asthma which are the triggers for the chronic airway inflammation and are raised in acute exacerbations and hence assessing eosinophil count is evidence of serological markers for Airway inflammation . Hence this study was undertaken in areas of Coimbatore where such studies are not done previously.

- In asthma patient, eosinophils are present in blood, sputum, bronchial lavage and bronchial biopsy specimens, and increase in number correlate with disease severity, airway obstruction and bronchial hyper reactivity.

- Atopy, the propensity to produce a higher amount of Ig E in response to allergens appear to be greatest risk

- Population studies have shown that majority of children and adults with asthma are atopic, though it may occur in few non atopic individuals with no positive skin tests or raised serum Ig E levels.

- Population studies have also shown that prevalence of asthma increase with increasing levels of Ig E and those with low levels of serum Ig E have low prevalence of asthma.

# AIMS AND OBJECTIVES

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# REVIEW OF LITERATURE

Bronchial asthma is an airway disease with episodic, reversible bronchial obstruction, interspersed with symptom free period. It is caused by increased responsiveness of tracheobronchial tree to various stimuli leading to spasmodic narrowing of airways . It is manifested clinically as paroxysms of wheeze, cough and dyspnea[01].

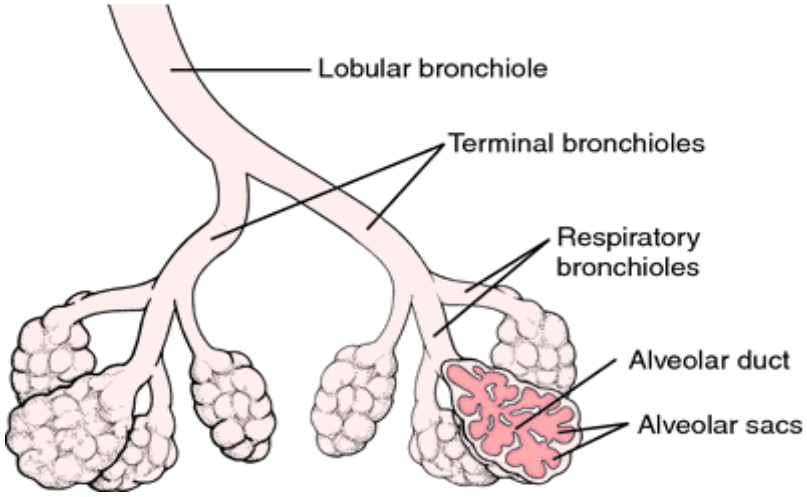



**Fig 1 : Normal Anatomy of airways**

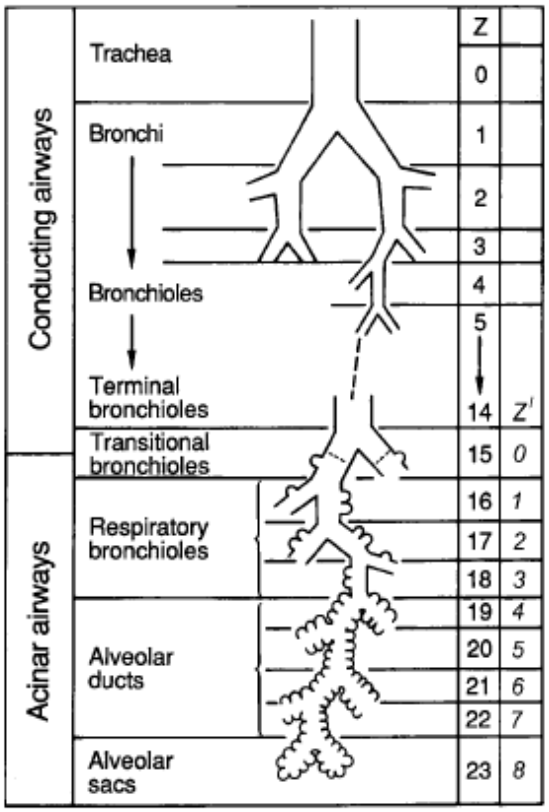



**Figure 2 : Conducting and non conducting airways**

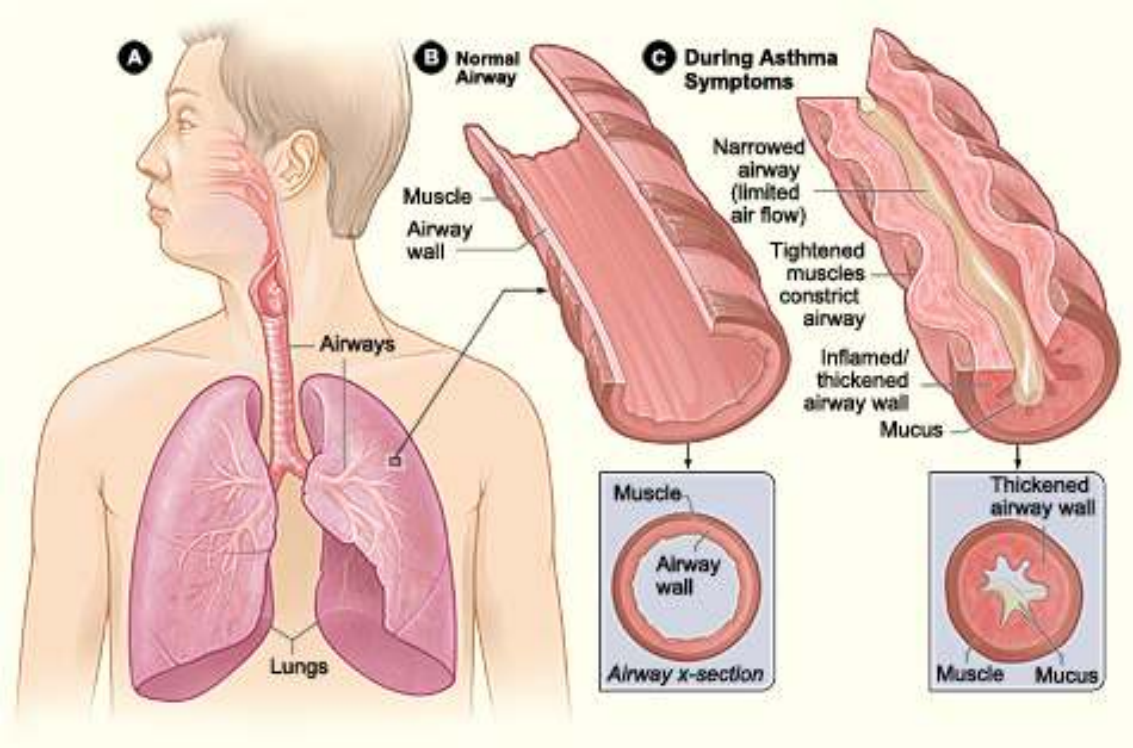



**Fig 3 : Airway in normal individuals and asthma**

**PREVALENCE**

Bronchial asthma is present world wide.It affects around 300 million people now across the globe. Its prevalence has increased in developed countries over 30 years and will increase by additional 100 million by 2015[02]. Nearly 10%adults and 15% children are affected by the disease. African americans are more likely than Caucasians to be admitted and have a higher mortality rate. Majority of patients in devoloped countries are atopic with allergic sensitizations to environmental allergens. Asthma is mostly complicated by smoking effects on lungs ,so it is difficult to be sure about the natural history of

disease in adults. Asthma can present at any age, with a peak at 3 years. In childhood, males are twice affected than females , but in adults the sex ratio equalizes. It is commonly believed that children "grow out of their asthma " . Long-term trials that have followed children until they reach 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life. Adults with Asthma including those with onset during adulthood, rarely become permanently asymptomatic. The severity of asthma does not vary significantly within a given patient; those with mild asthma rarely progress to more severe disease.

The International Study of Asthma and Allergies in Childhood (ISAAC)worked up prevalence of symptoms, specifically wheezing, in 13 to14 year aged in 155 centers throughout the world and prevalence rate was found ranging from <5% to nearly 40%. In United States ,at least one of every 20 individuals suffer from asthma. Over the last two decades its prevalence has increased 61%[03]. It is a leading cause of chronic illness in children. It causes nearly a loss of 10 million school days and 3 million work days. Since 1980, deaths from asthma has increased by 31%.

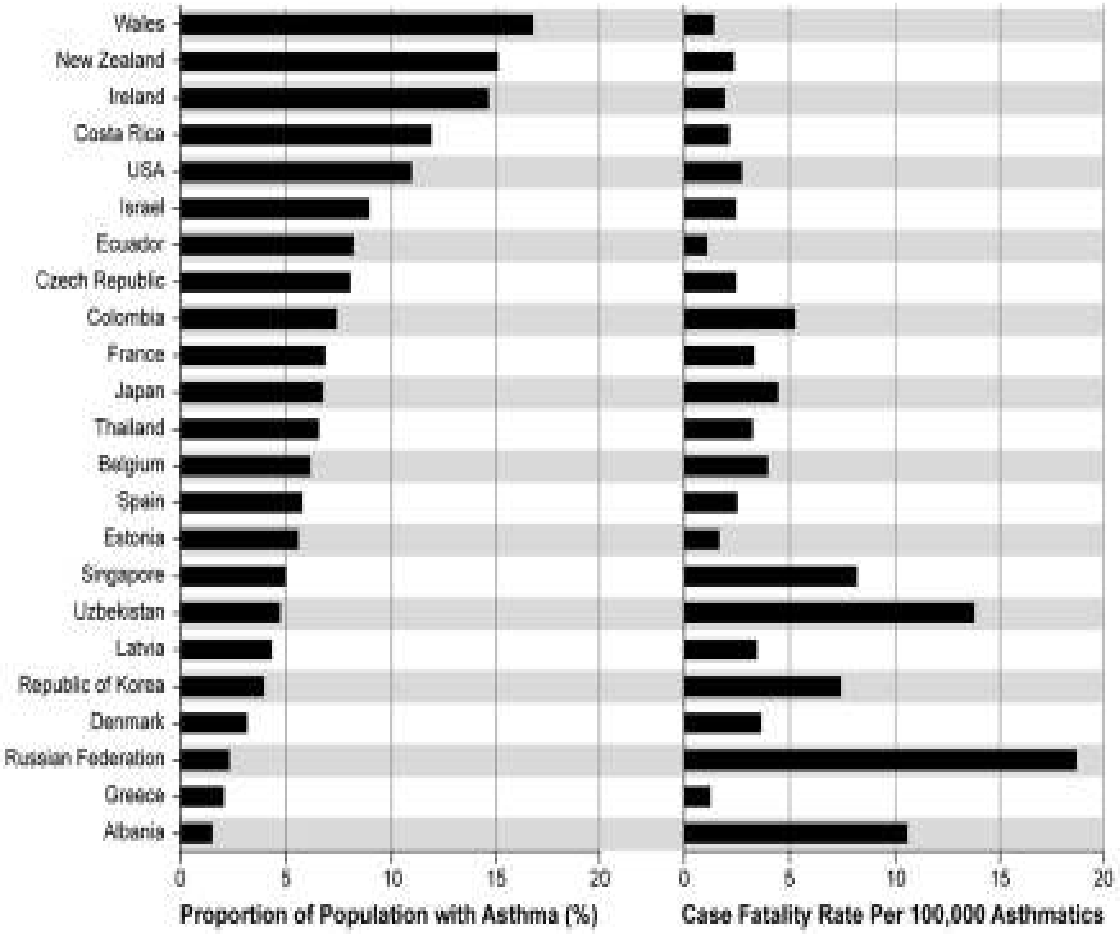



**Fig 4 : Prevalence and mortality worldwide**

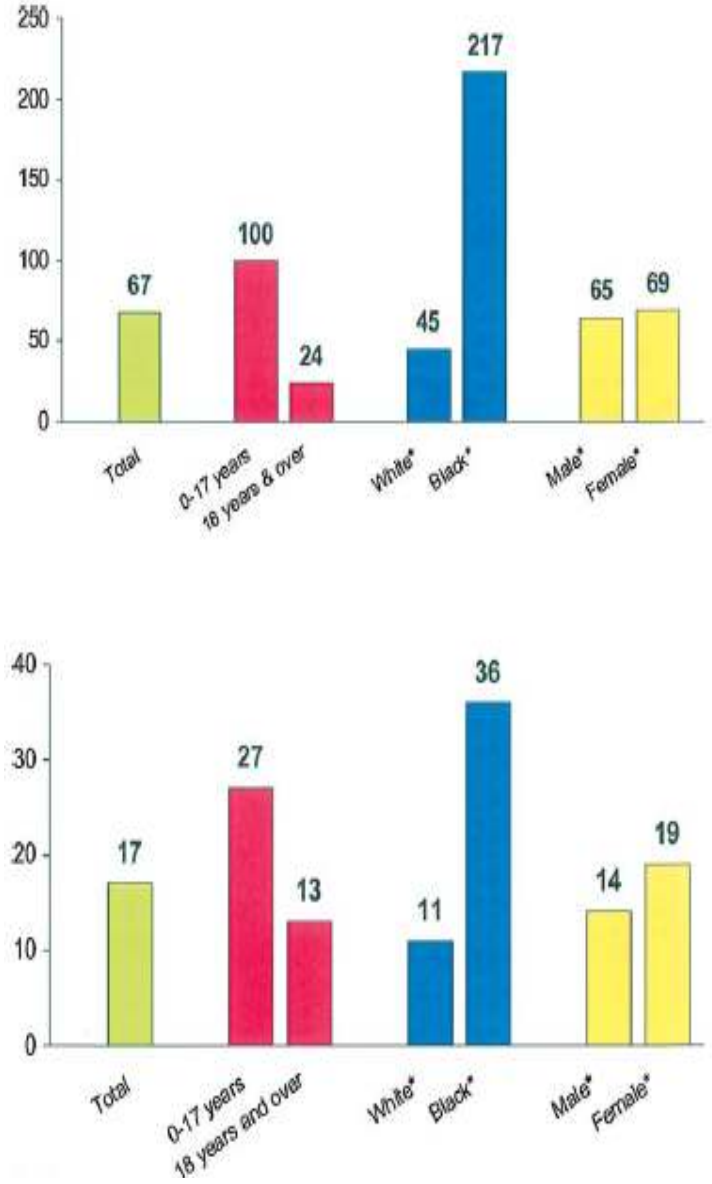



**Figure 5 :Asthma emergency department visits *(top)* and hospitalizations *(bottom)* per 10,000 populations, 2014. Hospitalizations are three time more frequent and emergency department visits almost five times more frequent among blacks. Hospitalizations are more frequent in children than adults. Source: National Hospital Ambulatory Medical Care Survey, National Center for Health Statistics, Centers for Disease Control , age adjusted to 2012 population.**

# HISTORY OF ASTHMA

The meaning of greek word asthma is “breath hard” /“to pant”[04]. Hippocrates was the first to recognize spasmodic nature of the disease and thought its onset was due to climate change and occupation.Malinonides, physician of the Sultan of Egypt in the 12th century believed that successful treatment of asthma required a thorough knowledge of patient, his hygiene, diet, medication, personal behavior etc. He also felt that mental factors could have an adverse effect on a patient’s physical health, including respiratory functions[02]. In the past asthma was synonymously used for dyspnea as well.

It was Henry Hyde Salt (1860) in his book “On Asthma, its Pathology and Treatment” gave a vivid comprehensive description and separated asthma from dyspnoea. He separated the idiopathic uncomplicated spasmodic asthma from symptomatic or complicated asthma (organic asthma). He recognized that the former arouse most commonly in childhood. He blamed inhalation of dust, hay, fur, feather and a large psychological overlay as well.In 1968 Sir Joh Flover in his book “A Treaties of Asthma’ have said asthma is due to the constriction of bronchi. He also distinguished between different types of asthma by contrasting continuous asthma with periodic or convulsive asthma. He also found that elements of the environment

could trigger asthma attacks.In 1862 the American thoracic society, New York defined bronchial asthma as disease characterized by an increased responsiveness of trachea and bronchi to various stimuli manifested by wide spread narrowing of airways that changes in severity either spontaneously or as a result of therapy" .In 1967 -short acting β 2 receptor agonist was discovered and was used in the treatment of asthma.In 1968, WHO officially declared IgE as 5th immunoglobulin isotype. and Sodium chlomoglycolate was introduced as a mast cell stabilizer thus offering a new approach to asthma management.In 1972- Inhaled steroids were introduced into the treatment of asthma as potent anti-inflammatory agent.In 1982- 83- Independent groups successfully identified the structure of the slow substance of anaphylaxis (SRS-A) believed to be the missing mediator of asthma. Nobel Prize was awarded for this discovery.

## ETIOLOGY

Asthma has both endogenous and environmental factors involved in its complex etiology. Among the endogenous factors atopy has been implicated as a major risk factor[02]. But even non atopic persons develop asthma though the risk is less. Most common allergens are house dust, animal fur, pollen grains. Atopy is due to increased Ig E production in response to allergens.

Apart from genetic factors, allergens, respiratory infections, indoor and outdoor air pollutants, even low maternal age and low birth weight ,duration of breast feeding and physical inactivity are associated in its etiology.

**Genetics of asthma:**

More than 100 genes are found to be be associated.

- Chromosome 5q is the most replicated susceptibility loci[05]
- Class II HLA alleles has been found to produce IgE response to ragweed pollen
- ADAM-33[06], a metalloproteinase produced by bronchial smooth muscles has been associated with airway hyperresponsiveness and bronchoconstriction.
- Mammalian chitinase -This enzyme triggers inflammatory mediators

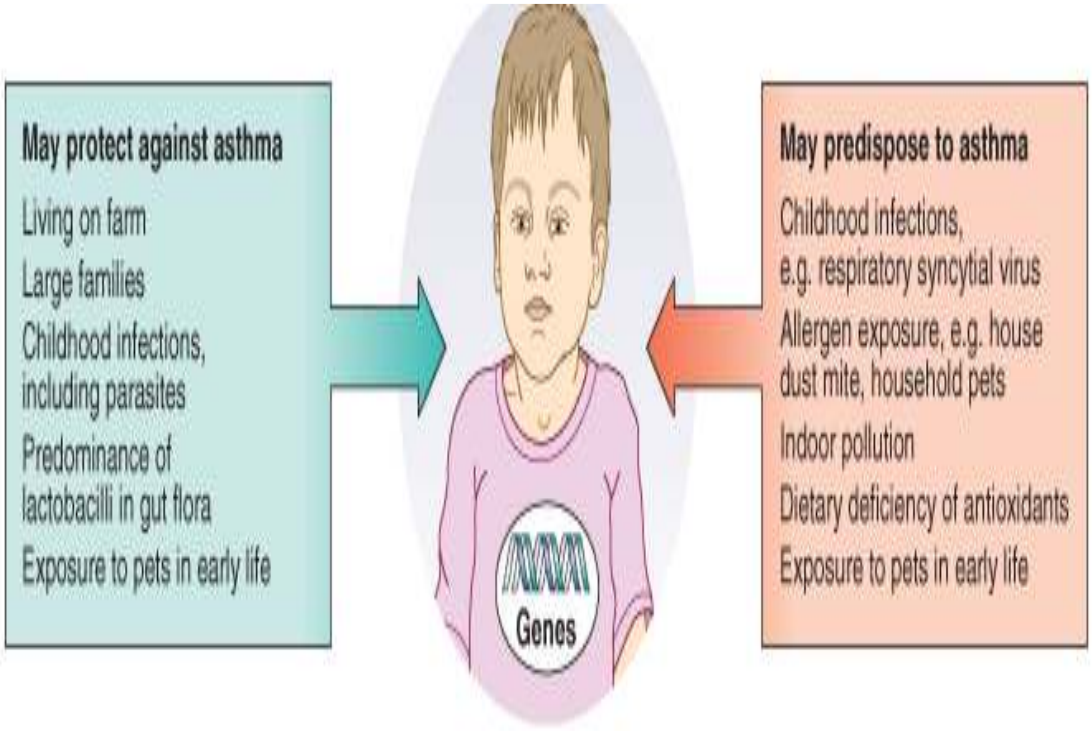



**Fig 6 : Protective and predisposing factors**

| **Endogenous Factors** | **Environmental Factors** |
|---|---|
| Genetic predisposition | Indoor allergens |
| Atopy | Outdoor allergens |
| Airway hyperresponsiveness | Occupational sensitizers |
| Gender | Passive smoking |
| Ethnicity? | Respiratory infections |
| Obesity? | |
| Early viral infections? | |
| **Triggers** | |
| Allergens | |
| Upper respiratory tract viral infections | |
| Exercise and hyperventilation | |
| Cold air | |
| Sulfur dioxide and irritant gases | |
| Drugs (β-blockers, aspirin) | |
| Stress | |
| Irritants (household sprays, paint fumes) | |

**Fig : 7 Etiology of asthma**

## RISK FACTORS FOR ACUTE SEVERE ASTHMA[07]

Keller et al had shown in his studies that in asthma of severe asthma, lack of private insurance and female sex all increase admission risk to hospital.

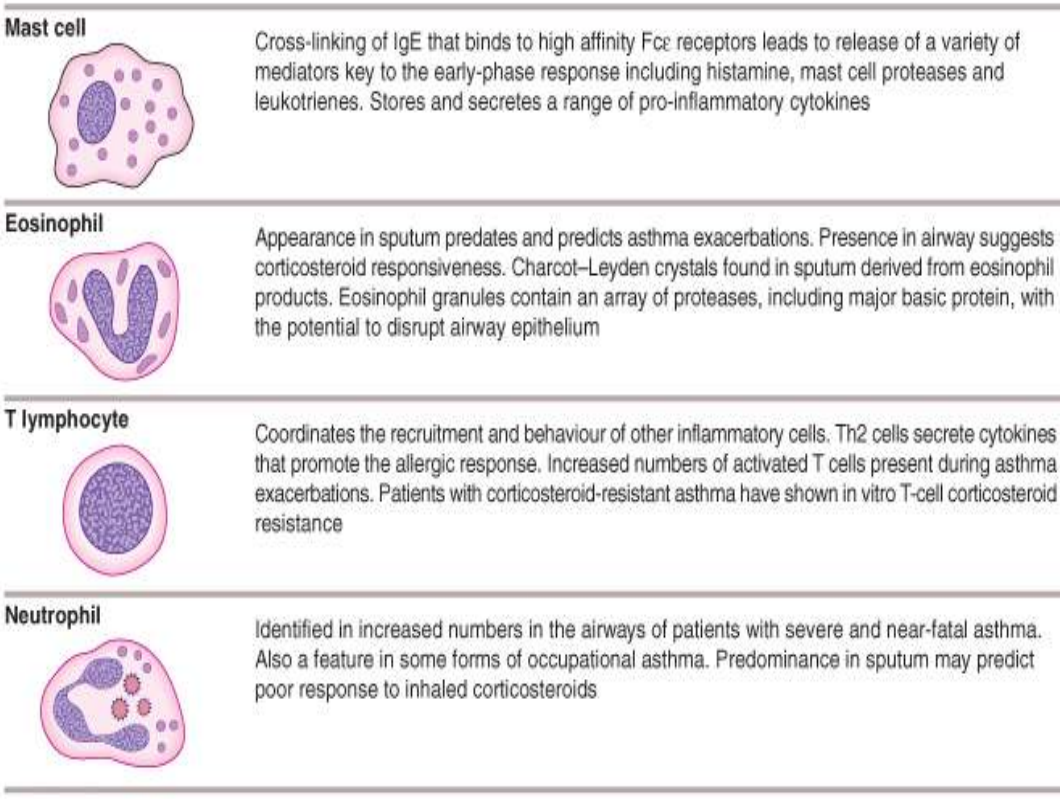
But studies by Robertson et al showed that,asthma of any severity in adults or children can lead to a fatal attack,both in children and adults. Nearly upto 13%adults and 23% children with mild asthma can have a life threatening attack of asthma. Various other precipitants requiring mechanical ventilation are

- Upper respiratory infection(61%)
- Exposure to Allergen/smoke
- Compliance related problems
- Drug abuse

In study of Keller Et al ,it was also noticed that age, race, month of admission ,smoking exposure in family and family history of atopy places a child at no higher risk for an intensive care admission. Chronic use of β2 agonists in asthmatic patients has been found to cause increased asthma related deaths.

## PATHOGENESIS [08]

- In asthma ,there is chronic inflammation of lower airway mucosa.
- Airway hyperresponsiveness ,which is the major physiological abnormality in asthma ,causes activation of mucosal mast cells and infiltration of mucosa with T lymphocyes and activated eosinophils.
- From trachea to terminal bronchioles inflammation occurs ,but cartilaginous airways like bronchi are mostly involved.
- Pathophysiology of asthma is complex mediated by interaction of several inflammatory cells leading to acute and chronic inflammation of airways.



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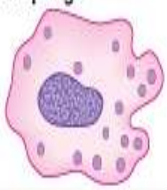
| **Macrophage**  | Secretes chemicals likely to be relevant to injury and repair including the secretion of growth factors that may be involved in airway wall remodelling |
| **Epithelium**  | Epithelial integrity disrupted, facilitating increased antigen translocation. Creola bodies (clumps of shed epithelial cells) and Curschmann's spirals (strips of desquamated epithelium) seen in biopsies from asthmatic patients. Participates in inflammatory response by secreting pro-inflammatory cytokines and growth factors. Increased mucus secretion and reduced mucociliary clearance. Subepithelial basement membrane thickened |
| **Airway smooth muscle**  | Undergoes hypertrophy and hyperplasia contributing to airway wall remodelling. Altered function contributes to airway hyper-reactivity. Secretes pro-inflammatory cytokines and growth factors |
| **Endothelium**  | Increased microvascular permeability contributes to increased mucus secretion. Expression of adhesion molecules promotes recruitment of inflammatory cells |
| **Neuronal dysfunction**  | Non-adrenergic non-cholinergic (NANC) nerves promote bronchodilatation; defects proposed as a potential mechanism of increased bronchial tone. Neuropeptides influence function of inflammatory cells. Remains unclear whether cholinergic mechanisms important in stable asthma but increased cholinergic tone a feature of acute asthma |

**Figure 8 : Cellular and structural components**

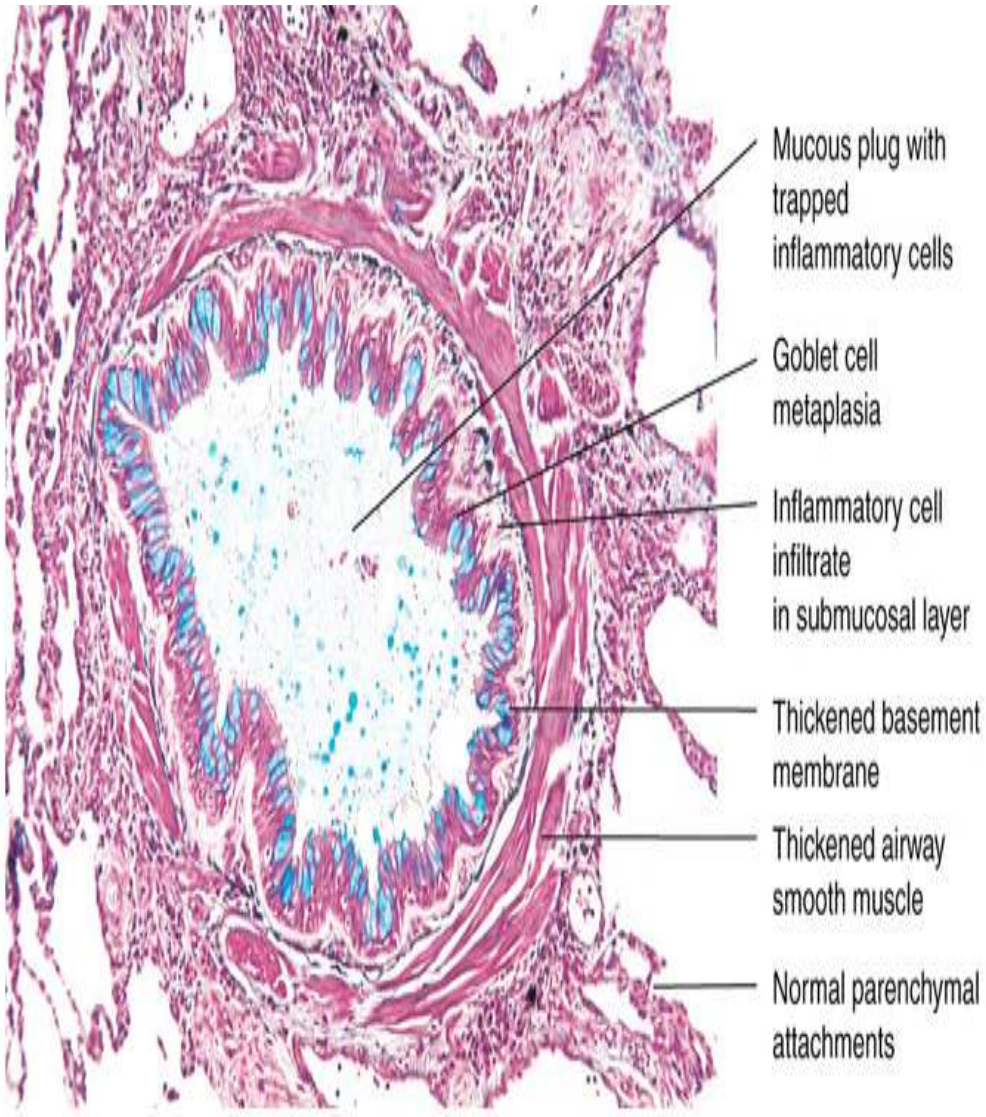



**Fig 9 : Histopathology Of Small Airway In Asthma**

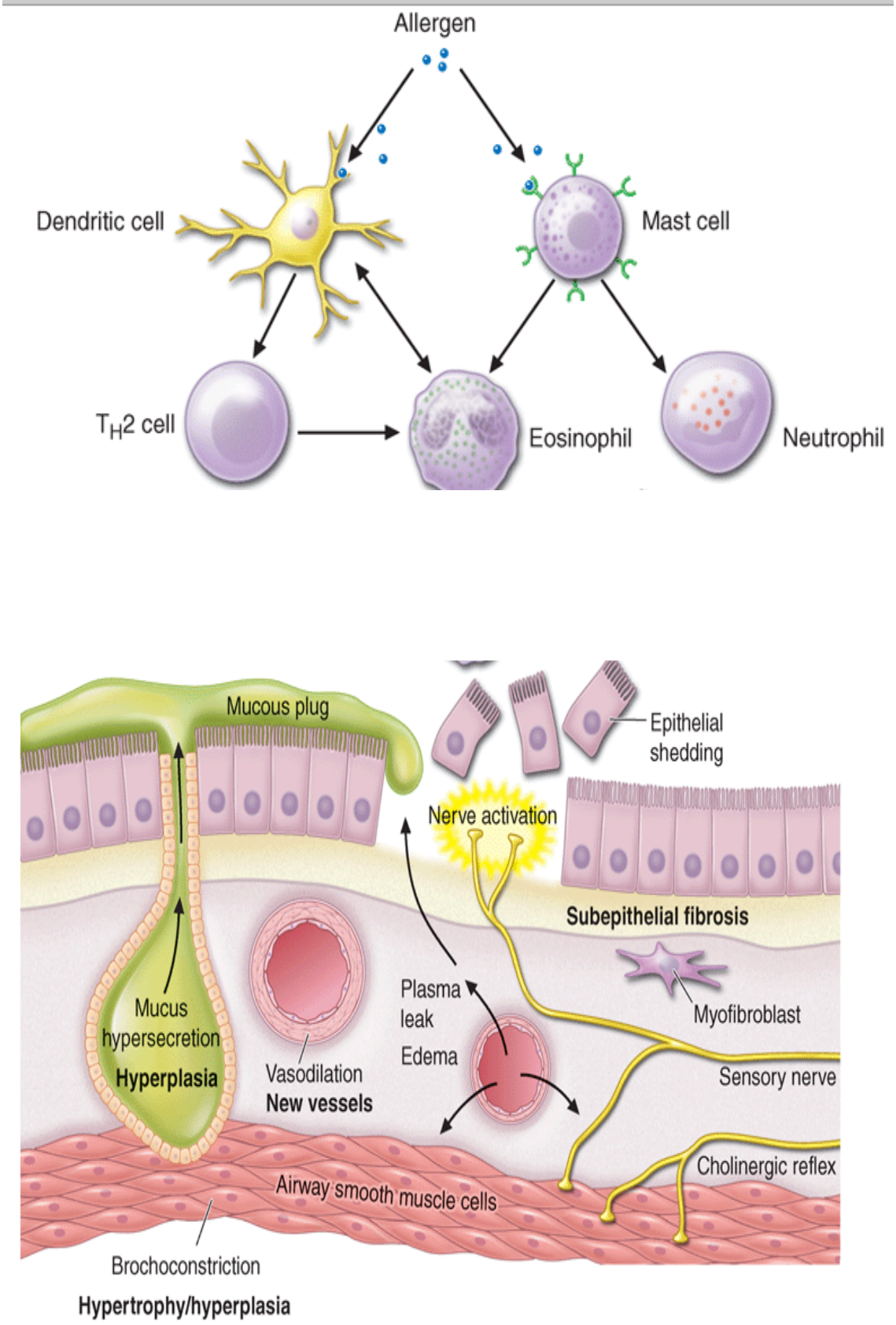



**Figure 10 : Pathogenesis of asthma**

When allergen is inhaled by an atopic patient , a two-phase bronchoconstrictor response is seen . Rapid interaction of allergen with mucosal mast cells occurs byan IgE mediated mechanism. Inflammatory mediators like histamine,prostaglandins,cytokines,chemokines cause increase microvascular leakage ,plasma exudation, increased mucus production forming viscid mucous plugs inturn causing airway obstruction, bronchospasm and attract various other inflammatory mediators.Airway remodelling occurs leading to changes in structure of airways finally causing irreversible airway narrowing and consequent decrease in lung function[09]. Increased airway smooth muscle,fibrosis, mucus hyperplasia are seen.

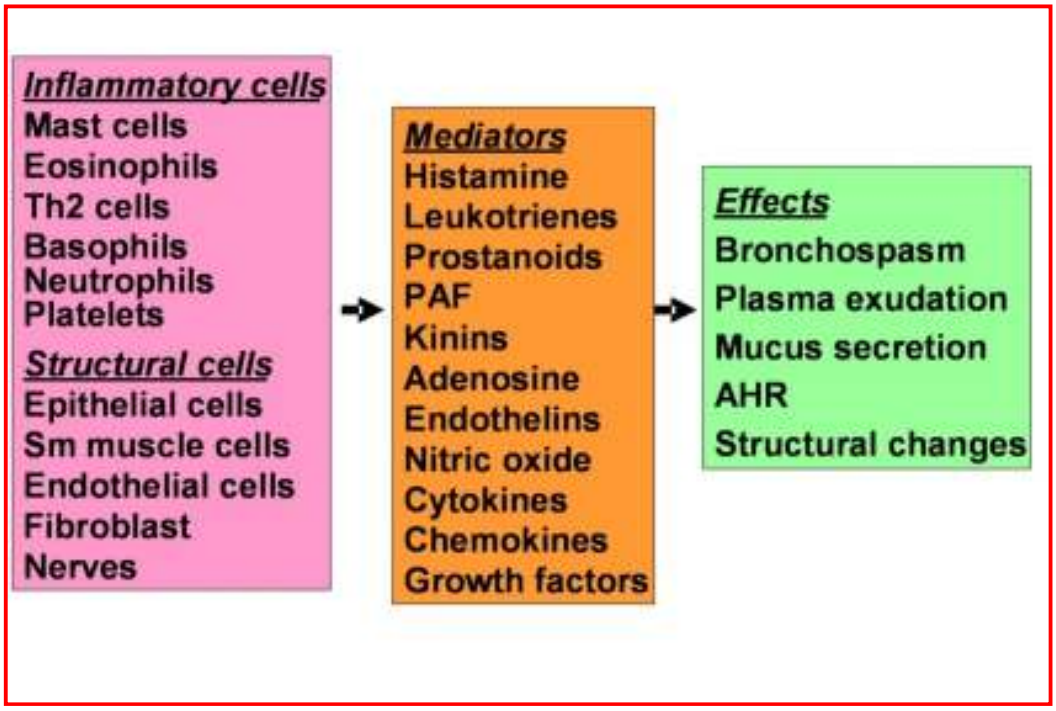



**Figure 11 : Inflammatory cells, mediators and effects**

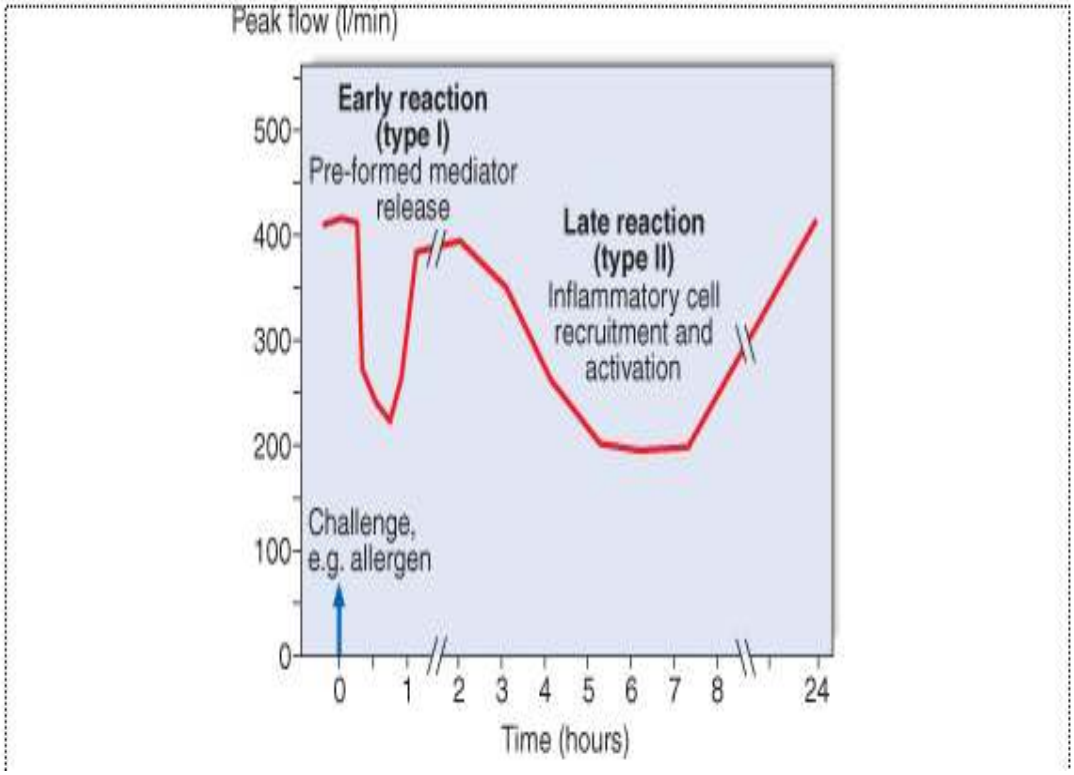



**Figure 12 : Hypersensitivity reaction in asthma**

# TYPES

## Atopic Asthma (Extrinsic asthma)

- Most common type of asthma also called early onset asthma[07].
- Dusts, pollens, cock roach or animal fur, and food are triggers.
- Members of family will have history

## Non-Atopic Asthma

- Skin tests are usually negative[07] though there is evidence of allergy sensitisation.
- In family members disease is unlikely.
- Respiratory infections caused by viruses can predispose.
- Pollutants of air also lead to this type of asthma.

## Drug-Induced Asthma

Many drugs can provoke asthma.

- Aspirin sensitive asthma[09], is seen in people who have polyps in nose and nasal obstruction, sneezing, rhinitis periodically.
- Mechanism is that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thus activating the bronchoconstrictor leukotrienes.
- Aspirin-sensitive asthma responds to usual therapy with ICS.
- Antileukotrienes are useful in these patients, they are no more effective than in allergic asthma.
- Rarely, aspirin desensitization is needed, but it should be undertaken only inspecialized center.


**Figure 13 : Drug induced asthma**

**Occupational Asthma**

- Fumes of petrochemicals and various chemicals can trigger asthma.
- Very less quantities of exposure can induce attack, but usually it occurs after repeated exposure.

- Type I hypersensitivity reaction lead to release of bronchoconstrictor substances[07].

| Agent | Occupation | Prevalence |
|---|---|---|
| **HIGH-MOLECULAR-WEIGHT COMPOUNDS** [†] | | |
| Animals | | |
| Laboratory animals (rats, mice, rabbits, guinea pigs) | Laboratory workers, veterinarians | Moderate |
| Chicken | Poultry workers | |
| Crab | Crab processing | Moderate |
| Prawns | Prawn processing | High |
| Hoya | Oyster farmers | High |
| River fly | Contact with riverside power plants | Low |
| Screwworm fly | Flight crews | High |
| Bee moth | Fish bait breeders | Moderate |
| Plants and vegetables | | |
| Grain dust | Grain handlers | |
| Wheat or rye flour | Bakers, millers | |
| Gum acacia | Printers | High |
| Biologic enzymes | | |
| *Bacillus subtilis* | Detergent industry | High |
| Trypsin | Plastics, pharmaceutical | High |
| Papain | Packing | High |

**Figure 14 : Occupation and asthma triggers**

# CLINICAL FEATURES

**Symptoms are**

- Widespread polyphonic wheeze - Expiratory wheeze is heard with mild bronchoconstriction, both inspiratory and expiratory in moderate and inspiratory in severe type.

- In near fatal asthma chest is silent.

- All wheezes are not due to asthma. Other disorders producing wheeze are chronic obstructive pulmonary disease, cardiac asthma, allergic bronchopulmonary aspergillosis, eosinophilic pneumonias, carcinoid tumors and recurrent pulmonary emboli.

**Nocturnal asthma**

- Total decrease of greater than 20% in FEV1 or PEFR.It may be the only manifestation of asthma.
- Mechanism
    - Due to early morning decrease in circulating adrenaline,
    - Increased vagal tone in early morning
    - Airway cooling at night time
    - Circadian changes in plasma cortisol levels(midnight to early morning fall in cortisol levels).

- Worsening of asthma after meals or dyspnea occurring only after meals due to gastroesophagal reflex is gastric asthma. Symptoms may be chronic unless controlled by appropriate therapy.

- Catamenial asthma occur in females at times of menstrual cycle.

**Exercise-induced Asthma**

- Heavy exertion, mainly in cold climate, is highly suggestive of exercise-induced asthma.
- Typically, patient experiences symptom at the end of exercise, rather than during exercise[08].
- Persistent cough following exercise, in absence of wheezing, may also be a sign of asthma.

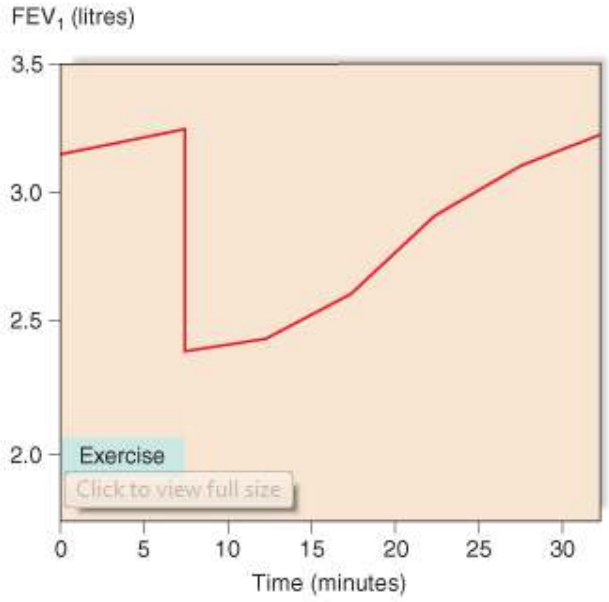



**Figure 15 : Exercise-induced asthma.**

**Aspirin induced asthma**-

- In contrast to classic atopic asthma, which patients usually develop before the age of 20, aspirin induced asthma typically occurs in individuals in the fourth decade of life.
- Thus, it appears to be an acquired disease[09].
- In general, these patients do not have a prior history of exposure and potential sensitization to NSAIDs.
- Familial predisposition is also rare; in one study, a positive family history was noted in only 2 of 500 patients.

**Associated conditions with asthma:**

- Rhinosinusitis with or without nasal polyps is mostly present and should be treated with saline rinsing, antihistamines and corticosteroids given intranasally[10].
- Vocal cord dysfunction can coexist with severe attacks of asthma. Speech therapy and behavioural therapy is beneficial.
- Obesity is well recognised as a comorbid condition and can worsen asthma control. It can be related to altered lung mechanisms, respiratory pattern, or increase in systemic inflammation. Obesity should be controlled by weight loss and exercise in such patients.
- There is no much variation in asthma prevalence as general population. Though there is no studies proving direct link between

tobacco use and development of asthma ,its use can make patients less responsive to corticosteroids and make it difficult to control. Therefore tobacco cessation should be encouraged in all patients.

- Symptomatic gastroesophagal reflex disease can cause cough and wheeze in few patients. Treatment with H2 blockers or proton pump inhibitors are useful. Empirical treatment of gastroesophagal reflex disease in such patients is not of use.
- Asthma may be difficult to control if associated with obstructive sleep apnea and should be assessed with overnight polysomnogram if there is suspicion.
- Approach to allergic rhinitis and asthma
- Atopy has a role in their co existence but it is not a prerequisite.

**1. When to suspect AR coexisting with BA?[11]**

- Recurrent sore throats
- Hoarseness of voice
- Snoring
- Persistent mouth breathing
- Pain/pressure over sinuses
- Persistent headaches
- Recurrent otitis media especially in children
- Cough especially in children
- Halitosis.
- Poor sleep and daytime fatigue

- Persistent respiratory symptoms inspite of controlled asthma and normal lung spirometry

**2. When to investigate AR with BA?**

- In poor asthma control in spite of appropriate treatment and good adherence
- Skin allergies or eczema which are difficult to treat
- Persistent nasal obstruction, congestion, postnasal drip, reduced smell sensation for >12 weeks[11]
- Persistent rhinitis which does not respond to a trial of intranasal corticosteroids
- Persistent epistaxis unilaterally-tumors,vasculitis or granuloma
- Diffuse nasal polyps with or without asthma history

**3. If any of above conditions are present, following tests are suggested[12]**

1. Repeat spirometry pre and post bronchodilator.
2. Routine haematological and radiological tests
3. Allergy tests-Skin prick tests or allergen specific Ig E/RAST
4. CT Scan to rule out intranasal pathology

**Acute severe asthma (Status asthmaticus)**

- It is a medical emergency.
- Patient is too dyspneic to speak, hypoxic and cyanosed due to severe bronchospasm.
- It is characterised by tachycardia, tachypnea[12], sweating, pulsus paradoxus, and altered level of consciousness.

- Fall in spirometry values are seen. Normal or rising PCO2 warns of an impending respiratory failure.It requires prompt monitoring and treatment.

- Chest Xray is not of much help, occasionally pneumothorax or pneumonia may be present.

- Spirometric values will fall, PEF will be < 40% predicted.

**Severity level assessment of acute asthma excacerbation**

**Near fatal asthma**-High or rising PC02 ,On ventillatory support

**Life threatening asthma -**

- Peak expiratory flow of <33% based unpredicted as P02< 92%, Pa02 < 60mm Hg[12]
- Normal PaC02 35-45 mm Hg
- Silent chest
- Cyanosis
- Feeble respiratory effort
- Bradycardia
- Dysrhythmia
- Hypotension
- Exhaustion
- Drowsiness
- Confusion
- Coma

# REFRACTORY ASTHMA

- This category includes patients, not attaining relief even with high dose of inhalations

## CAUSES OF REFRACTORY ASTHMA

1.Upper airway obstruction[11]

a)Tumors

b)Epiglottitis

c) Vocal cord dysfunction

d) Obstructive sleep apnea

2.Tracheomalacia

3.Endobronchial leision

4.Foreign body

5.Congestive cardiac failure

6.Gastroesophagal reflex

7.Sinusitis

8.Herpetic tracheobronchitis

9.Adverse drug reaction

- Aspirin
- Angiotensin converting enzyme inhibitors
- Inhaled pentamidine

10.Allergic bronchopulmonary aspergillosis

11.Hyperventillation with panic attacks

**DIFFERENTIAL DIAGNOSIS BASED ON HISTORY AND CLINICAL FINDINGS**

| HISTORY | POSSIBLE DIAGNOSIS |
|---|---|
| • Symptomatic since birth | 1. Cystic fibrosis[12]<br>2. Primary Ciliary dyskinesia.<br>3. Gastroesophagal reflex. |
| • Positive family history of uncommon airway disease | 1. Cystic fibrosis.<br>2. Airway or lung malformation |
| • Acute onset with no prexisting problems | 1. Aspiration of foreign body |
| **SYMPTOMS** | |
| • Upper airway symptoms,fever | Acute airway infection<br>• Bronchitis<br>• Bronchiolitis<br>• Pneumonia |
| • Dysphagia,heart burn,vomiting, cough | Aspiration,GERD |
| • Abnormal hoarseness of voice | Laryngeal or vocal cord disease |
| • Inspiratory and expiratory stridor | 1.Laryngitis<br>2.Tracheitis<br>3.Laryngomalacia/tracheomalacia |

| | |
|---|---|
| • Failure to thrive | Cystic fibrosis,immune deficiency<br><br>Lung malformation |
| • Sleep predominant symptoms | Upper airway disease(post nasal drip, GERD) |

**Complications of asthma**

- Patient goes to dehydrated state.
- Infection of airways [13]
- Tussive syncope
- Rarely pneumothorax
- Respiratory failure .

# INVESTIGATIONS

**Chest Xray**

Usually normal except in severe cases, when there is hyperinflated lung fields.

**Blood tests**

1. Peripheral blood eosinophil count:

- Absolute eosinophil count (greater than 4 percent or 300 to 400 permm3) may be seen in both allergic and nonallergicasthmatics[15].

- When present, eosinophilia may be usedto support a diagnosis of asthma; however, its absence is of no value in excluding asthma[16].

- Unusually high eosinophil counts (greater than 800 permm 3) suggest the presence of otherdisorders, such as allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, tropical eosinophilia, and Loeffler's syndrome.

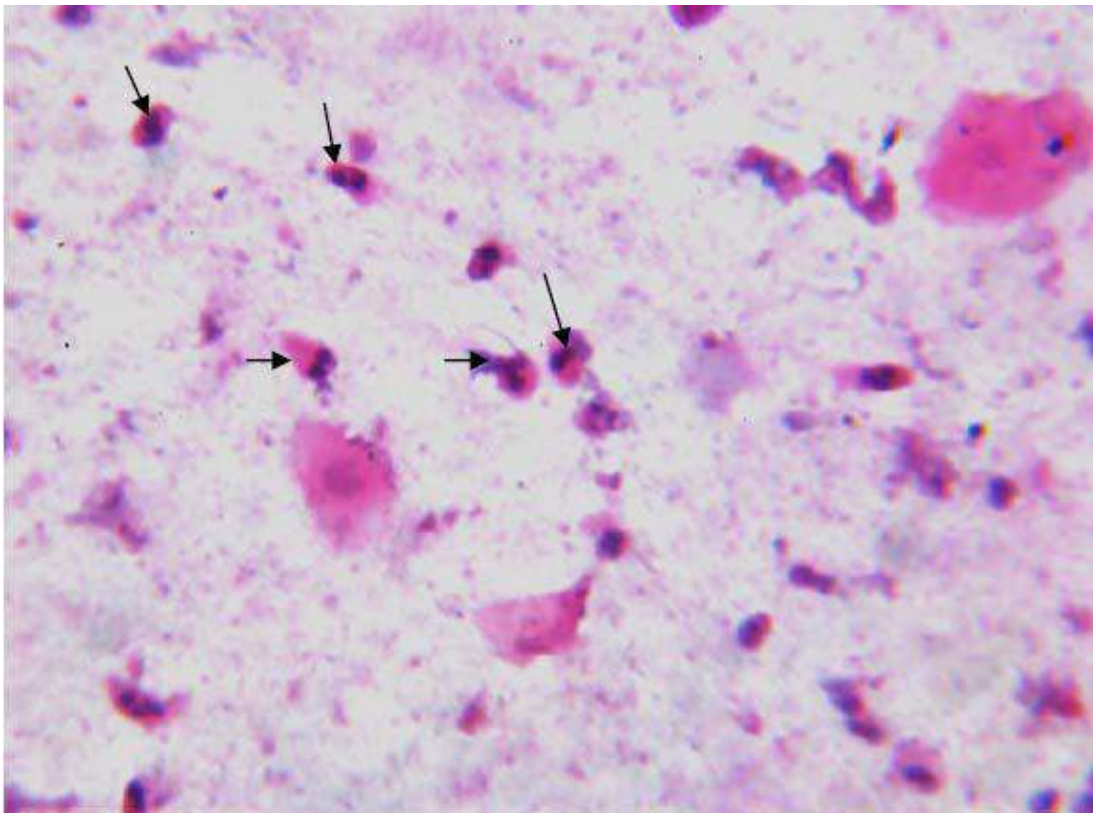


**Figure 16 : Eosinophils under light microscopy**

## SERUM IgE

- Epidemiologic studies have demonstrated an association between asthma and total serum immunoglobulin E (IgE) levels, standardized for age and sex.

- Whether this association signifies that aeroallergens are prominent etiological factors, or that immunologic processes in the pathogenesis of asthma are capable of stimulating IgE production[19] as an unrelated phenomenon needs further definition.

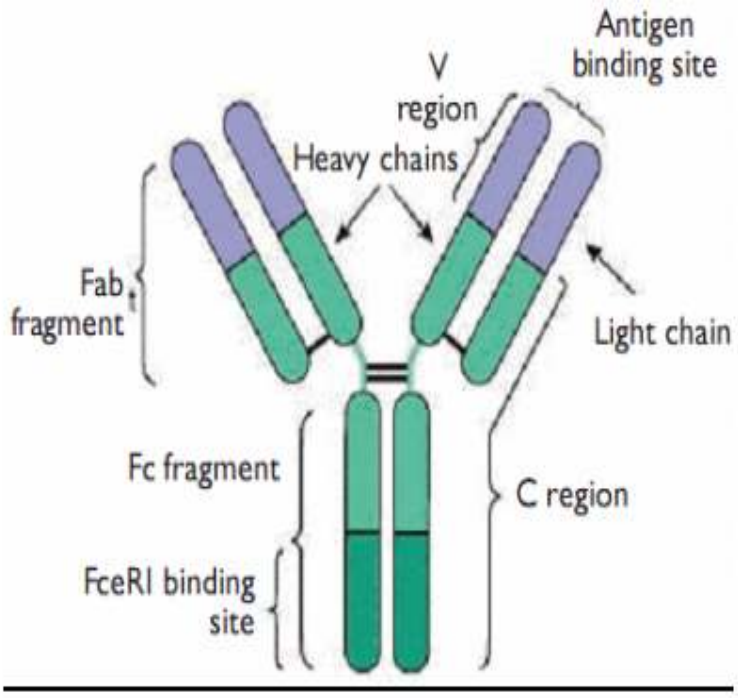



**Figure 17 : Structure of IgE**

- Studies have also shown a relationship between total serum IgE and asthma in patients with negative skin tests.
- In addition, other studies have reported that elevations in total IgE are strongly associated with asthma, whereas skin test reactivity is more closely related to allergic rhinitis [20].
- Importantly, IgE levels are used to calculate the dose of the anti-IgE antibody omalizumab,when it is used for asthma treatment
- It should be noted that eosinophilia[21] may not be present if the patient is taking corticosteroid

**Sputum Examination**

In research studies ,sputum eosinophil counts have been shown to predict clinical outcomes, particularly exacerbations when corticosteroids are withdrawn, but more research needs to be done before sputum examination can be used as diagnostic tool.

**Allergy Tests**

Tests to determine whether the patient is allergic and to investigate the role of specific allergens as a cause of asthma are of value in some patients.

In selected populations, evaluations for perennial or indoor allergens, such as dust mite, cockroach, or animal dander have become increasingly important.

A study done by Das B.K., Kumar S.. Panda B.K.. Misira O.P in which serum IgE levels were estimated in patients presenting with wheezing and to identify the potential cases of asthma on the basis of raised IgE levels. In this study, they found that mean serum IgE was significantly higher in asthma patients ($p < 0.001$). In conclusion, they reported that determination of serum IgE may be of value in identifying those children presenting with first attack of wheezing who may develop asthma in future and these cases needs long term follow up for of conclusion.

In a study done by Saha O.K, Modaka Batabayal S.K., Choudhari D.K,Maitra S.B. et al about clinical significance of IgE in bronchial asthma, total mean serum IgE[22] levels of 63 patients, suffering from bronchial asthma and 64 control subjects were estimated. Mean serum IgE level of patients and control subjects was 643-1125 I U/ml and 10-100U/ml respectively.

**PULMONARY FUNCTION TESTS [23]:**

John Hutchison, a surgeon recognised that the volume of air that can be exhaled from fully inflated lungs is a power indicator of longevity.

He invented the spirometer to measure what he called vital capacity, ie, capacity to live. Later concept of timed vital capacity, known as forced expiratory volume in one second (FEV1) was added. Since then pulmonary function tests has become important aspect of evaluation of respiratory diseases.

**Clinical use of spirometry are**

- To make a diagnosis based on lung function
- Assess patients treatment response.
- Pre operative pulmonary evaluation
- Detection of pulmonary function abnormality in predisposed individuals, eg: occupational exposure, neuromuscular, chest wall or upper airway disorders
- Most important component in successful pulmonary function testing is a well motivated and enthusiastic technician.He should also be well trained and experienced
- At least three repeat testing is necessary is important for proper interpretation of results.

**CONTRAINDICATIONS OF SPIROMETRY**

- Post myocardial infarction upto one month
- Chest/abdominal colic
- Cognitive impairment

**Types of spirometers of 2 types**

1. Volume displacement spirometers
2. Flow sensing spirometers

Flow sensing spirometers are mostly used as they are portable and easy to maintain. They are either pneumotach based or turbine based.

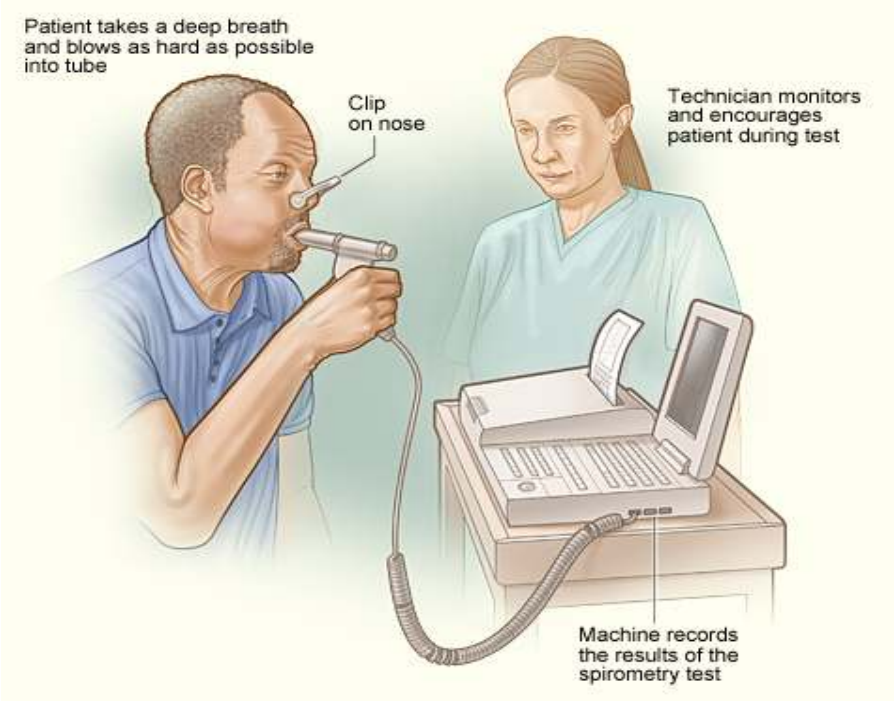



**Figure 18: Performing Spirometry**

**Expiratory manoeuvre**

- Take a full deep,breathe away from spirometer
- Hold the mouth piece between lips to create a good seal
- Fastly and hardly expire until no breathe is left

**Expiratory and inspiratory manuevre**

- Hold the mouth piece between the lips to get a good seal

- Breathe in and out for 2-3 tidal breaths
- Expire as fast and as hard as possible for as long as possible until no breathe is left
- Inspire rapidly to a maximum capacity

Spirometry should be repeated again 15-30 minutes after administration of short acting beta agonist, 200-400mcg of salbutamol,to check for bronchodilator reversibility.

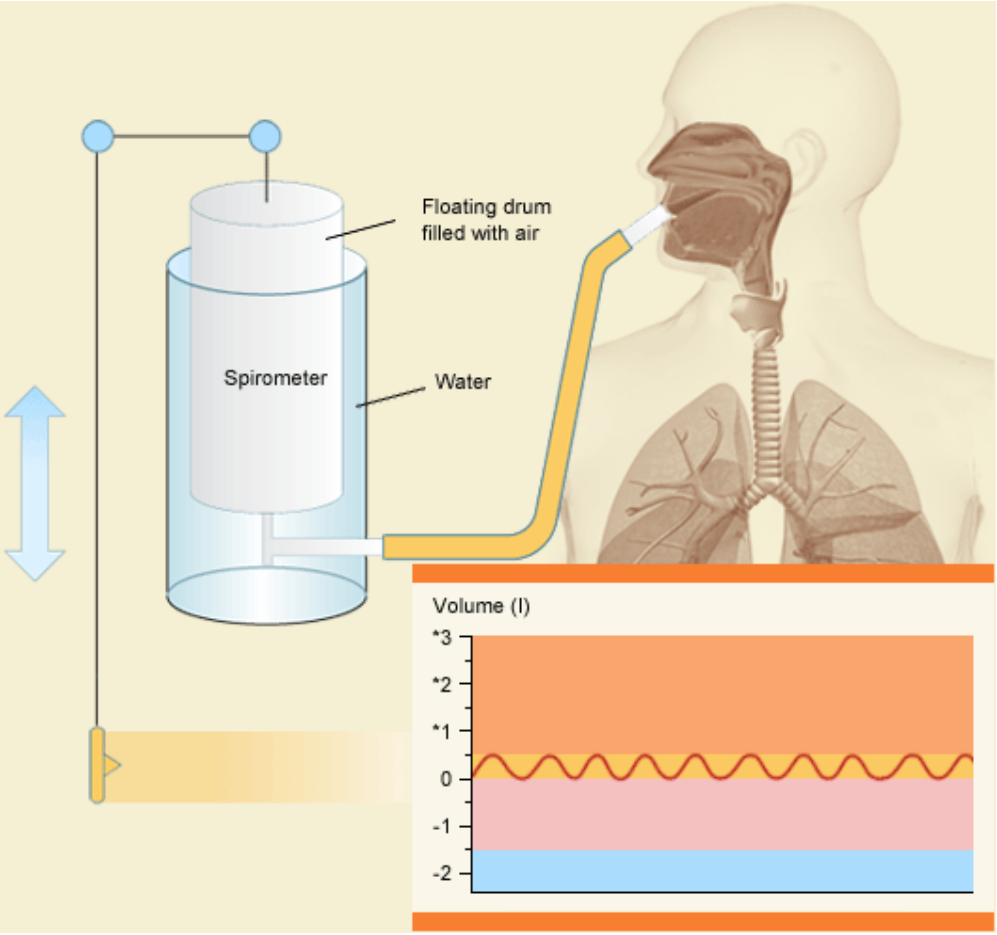



**Figure 19 : How a spirometry works?**

A spirometer records movement of lid,which moves upwards when patient inspires and downwards when expires. It can measure tidal volume,inspiratory reserve volume,inspiratory capacity,expiratory reserve volume and vital capacity.

**Recording Spirometry**[23]

Recorded both graphically and numerically

Graphically it is recorded as

- **Volume versus time (Spirogram)**
- **Flow rate versus volume**

Flow volume curve when only expiratory flow is recorded Flow volume loop when inspiratory flow is also recorded.

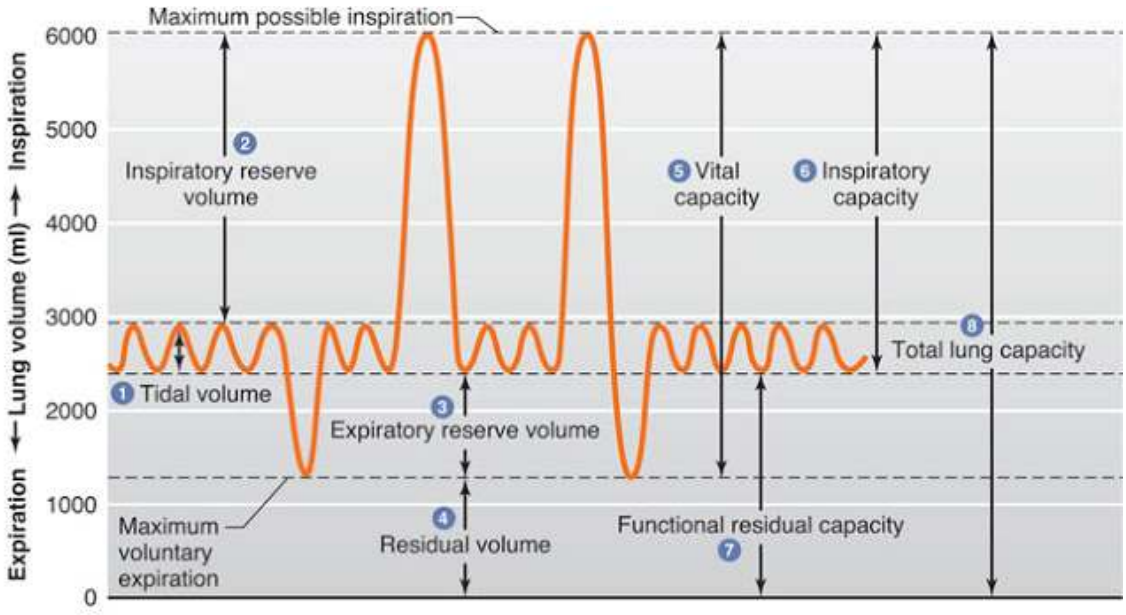



**Figure 20 : Lung capacities**

**1. Tidal volume – 500ml,** It is the air that moves into the lung with each normal inspiration or the volume of air that moves out of the lung with each normal expiration.

2. **Inspiratory reserve volume** – 3300 ml, The air inspired with a maximal inspiratory effort in excess of tidal volume.

3.**Expiratory reserve volume-1000 m**l,Air expelled with a maximal expiratory effort in excess of tidal volume.

4.**Residual volume– 1200 ml**,Amount o air remaining in the lungs even after forced expiration

5.**Inspiratory capacity- TV+ IRV, 3800 ml**,Total amount of air that can be breathed in.

6.**Vital capacity-IC+ERV,4800 ml**,Maximum amount of air that can be expelled out forcefully after a maximal deep inspiration.

7.**Functional residual capacity-2200**ml,Volume of air remaining in the lung after normal expiration.

8.**Total lung capacity-6000 ml,**Amount of air present in the lung after maximal inspiration.Maximum volume to which lungs can be expanded[23].

**Respiratory minute volume-6litres/min**

- Alveolar ventilation -4.2litres/min, Amount of air utilized for gaseous exchange every minute,
- Alveolar ventillatin=(Tidal volume – Dead space volume)x Respiratory rate
- **FEV1**-Forced expiratory volume in 1st second, It is the fraction of vital capacity expired during 1st second first second of forced expiration [23].

Also known as timed vital capacity.

In normal person FEV1 is 75 to 85%, FEV1 is more sensitive than vital capacity because in the early stages of many chronic diseases(eg-emphysema),vital capacity may remain normal, but the FEV1 begins to fall from very beginning.

Resistance to small airways is best measured by maximum mid expiratory flow rate followed by FEV1[19]. In early obstructive disease which originates in small airways FEV1/FVC may be normal but FEF 25-75%. Maximum midexpiratory flow rate is the average expiratory flow rate during the middle 50% of the vital capacity. It is also called FEF25-75%.

Hallmark of obstructive lung diseases is a decrease in FEV1/FVC.

**Spirometry in asthma**

Asthma is characterised by obstructive abnormality with good bronchodilator reversal. Assessment of asthma severity (Global Initiative On Asthma-GINA guidelines) is necessary for recommended step care approach to management of asthma.

Asthma severity based on spirometry is classified as follows

**Severity**

1.Intermittent $\geq 80\%$

2.Mild persistent $\geq 80\%$

3.Moderate persistent 60-80%

4.Severe persistent $\leq 60\%$

**Spirometry in restrictive abnormality**

Restrictive abnormality occurs due to chest wall diseases,pleural diseases, parenchymal and interstitial lung diseases.Characteristic pattern of restrictive abnormality is reduced forced vital capacity

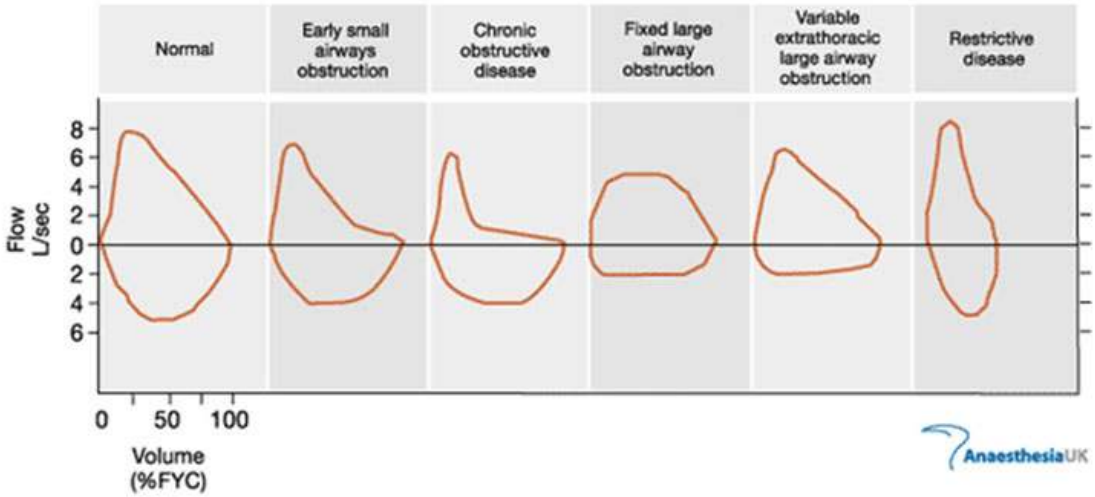



**Figure 21: Flow volume loop in different airway pathologies**

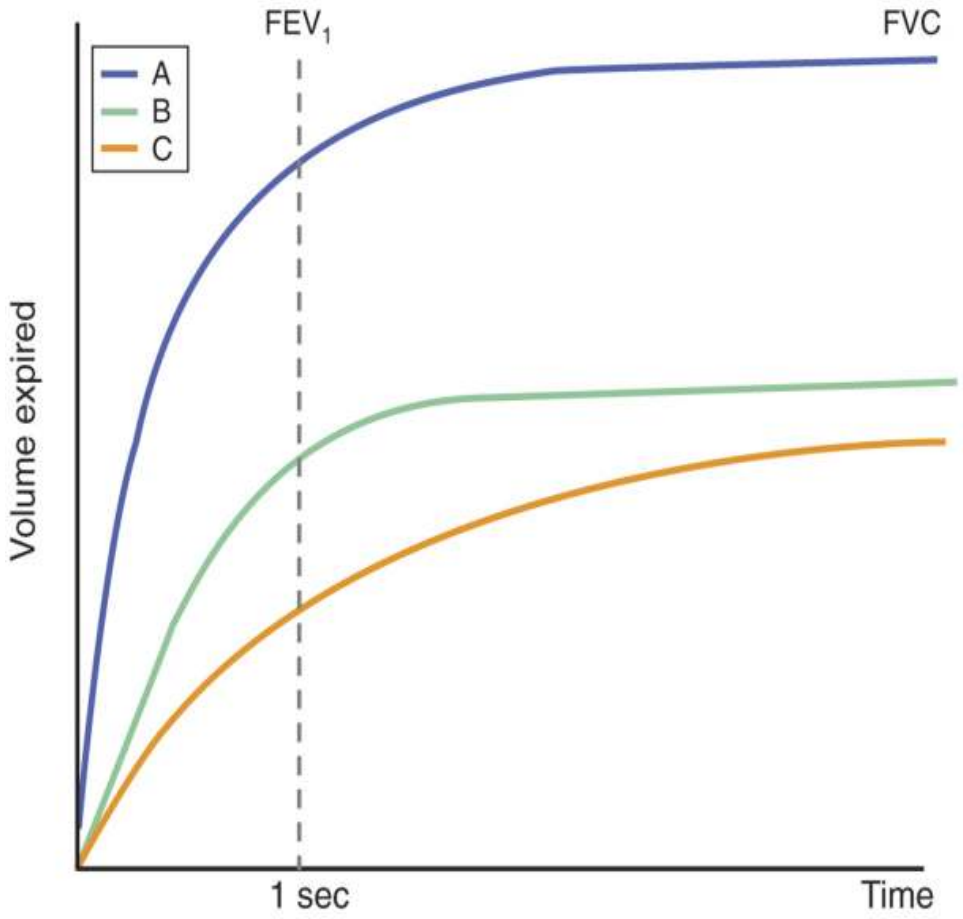



**Figure 22 : Comparison of spirometry - normal patient (A)and , restrictive defect (B), obstructive defect (C).**

## DIAGNOSIS OF ASTHMA

- $FEV_1$ ≥ 15% (and 200 ml) increase following administration of a bronchodilator/trial of corticosteroids
- > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on PEF diary
- $FEV_1$ ≥ 15% decrease after 6 mins of exercise

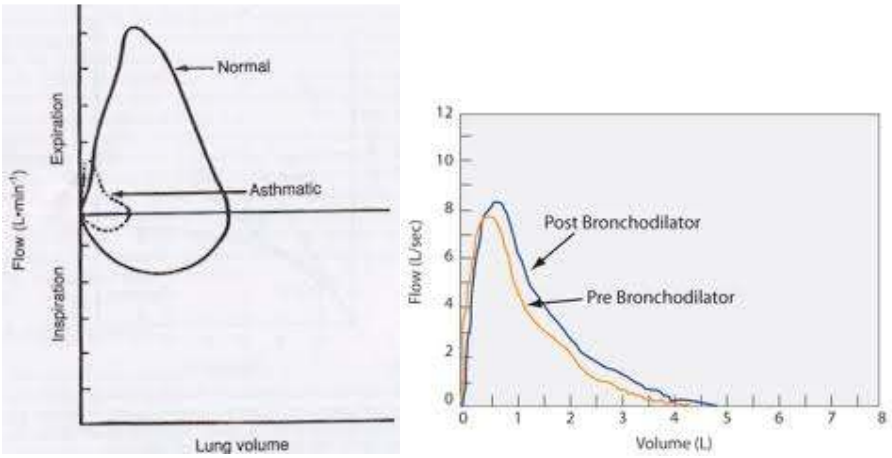
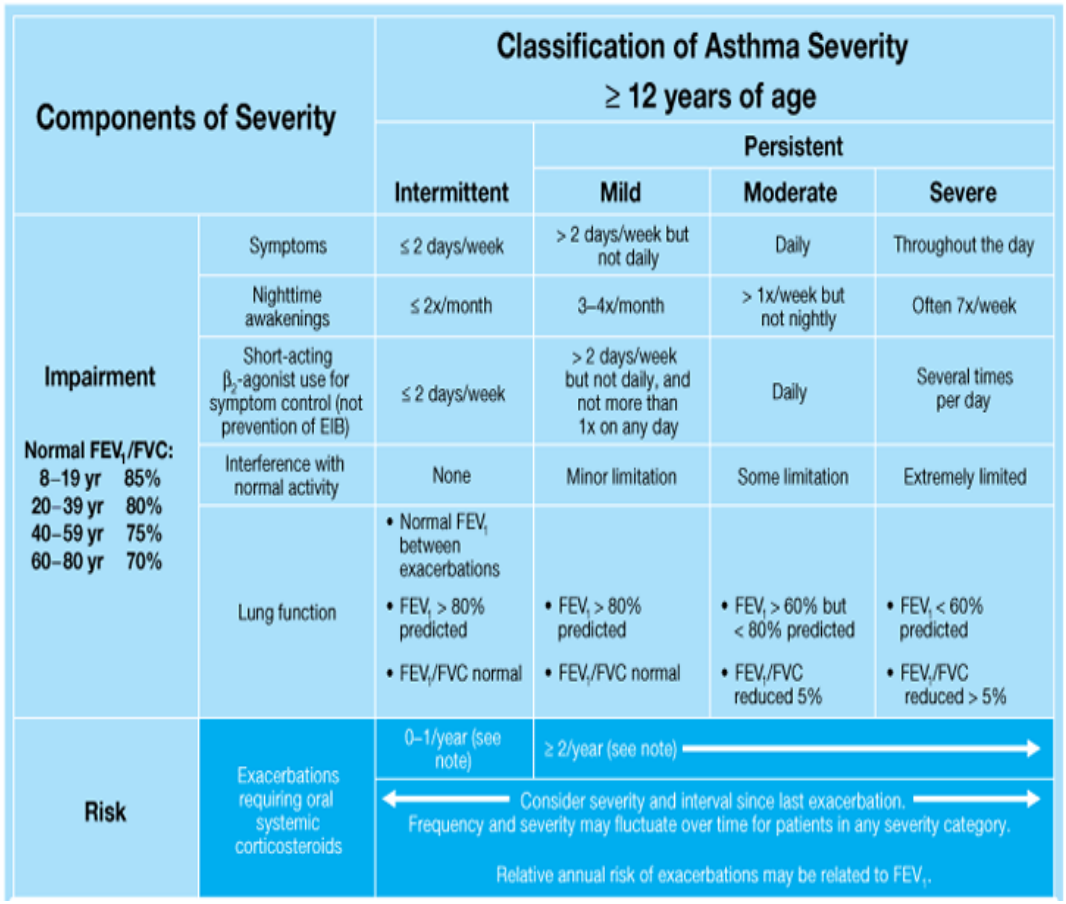



**Figure 23: Spirometry in asthma-Pre and post bronchodilator reversibility**



| Components of Severity | | Classification of Asthma Severity ≥ 12 years of age | | | |
|---|---|---|---|---|---|
| | | | Persistent | | |
| | | Intermittent | Mild | Moderate | Severe |
| Impairment<br><br>Normal $FEV_1/FVC$:<br>8–19 yr 85%<br>20–39 yr 80%<br>40–59 yr 75%<br>60–80 yr 70% | Symptoms | ≤ 2 days/week | > 2 days/week but not daily | Daily | Throughout the day |
| | Nighttime awakenings | ≤ 2x/month | 3–4x/month | > 1x/week but not nightly | Often 7x/week |
| | Short-acting $\beta_2$-agonist use for symptom control (not prevention of EIB) | ≤ 2 days/week | > 2 days/week but not daily, and not more than 1x on any day | Daily | Several times per day |
| | Interference with normal activity | None | Minor limitation | Some limitation | Extremely limited |
| | Lung function | • Normal $FEV_1$ between exacerbations<br>• $FEV_1$ > 80% predicted<br>• $FEV_1/FVC$ normal | • $FEV_1$ > 80% predicted<br>• $FEV_1/FVC$ normal | • $FEV_1$ > 60% but < 80% predicted<br>• $FEV_1/FVC$ reduced 5% | • $FEV_1$ < 60% predicted<br>• $FEV_1/FVC$ reduced > 5% |
| Risk | Exacerbations requiring oral systemic corticosteroids | 0–1/year (see note) | ≥ 2/year (see note) → | | |
| | | ← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to $FEV_1$. | | | |

**Figure 24 : Classification of asthma severity**

## MANAGEMENT OF ASTHMA

Successful management of the asthmatic patient requires an appreciation of two basic principles.

- First, asthma shows considerable heterogeneity
- In each patient, symptom severity may vary . Few may have a remission during adolescence, only to have them recur with even greater severity later in life.Intercurrent excacerbations that arise due to seasonal allergies or infection are common inasthma.
- Thus, the patientshould be monitored regularly, and treatment should be modified on an ongoing basis to meet the patient's current needs.

## AIMS OF ASTHMA THERAPY

- Minimal or no chronic symptoms,including nocturnal
- Minimal excacerbations
- No emergency visits
- Minimal use of required beta 2 agonist
- No limitations on activities including exercise
- Near normal PEF
- Peak expiratory flow circadian variation <20%

## CHRONIC STABLE ASTHMA

### Nonpharmacologic Therapy

❖ **Patient Education**

- Counselling the patient about the disease, its nature and risk factors and environmental control programs are effective in reducing morbidity as proven by many studies, but additional research is needed to decide which methods are the most effective and which groups of patients are benefitted the most.

- Improving patient understanding of the disease and its management and, thereby improving patient compliance to treatment is the aim.

- Another aim is engaging patient in self management practices, especially in terms of identifying and avoiding asthma triggers and recognizing and treating excacerbations of asthma in their earliest stages.

- Result in better control and decreased emergencies and hospitalizations due to asthma. The success of education programs is, to a large extent, dependent on their format

- Personal contact with a physician is considered superior to providing either audiovisual or written materials

Enquiry into over 200 asthma deaths in a study in United kingdom has proven that risk factors, medical management and patients behavioural and psychosocial factors were associated with fatal and near fatal events in asthma. Most deaths occurred before hospitalisation. Most patients who died had severe asthma, but a few also suffered from mild to moderate background disease. Most deaths occurred in inadequately monitored and those who were not on regular drugs.

**Adverse behavioural or psychosocial factors**

- Non compliance with treatment on monitoring
- Failure to attend clinic appointments
- Self discharge from hospital
- Depression, psychosis or other illness
- Alcohol or other substance abuse
- Obesity
- Learning difficulties
- Employment problems
- Income problems
- Childhood abuse
- Social isolation

All patients having severe asthma should have an agreed written action plan ,doing regular pulmonary function tests ,regular checking of inhaler technique and compliance.

❖ **Environmental Measures**

- Another important part of the management plan for all asthmatics is environmental measures

- Avoidance of air borne allergens, viral respiratory pathogens, air pollutants, and certain drugs can prevent exacerbations, reduce the need for drug treatment

- Avoidance of factors that may contribute to longer-term, airway inflammation responsible for abnormal airway responsiveness.

- Allergens from house dust mites, cockroaches, moulds, and pets, particularly cats and dogs, have been associated with asthma.

**PHARMACOLOGICAL MEASURES**

**BRONCHODILATORS**

- Act primarily on smooth muscles of airways

- Provide fast relief but not anti inflammatory

.

- 3 classes of bronchodilators are used:

  $\beta_2$ -ADRENERGIC AGONISTS

- They activate 2 adrenergic receptors seen in airways.

**Mechanism of action**

- Its primary action is relaxation of both proximal and distal airway smooth muscles preventing bronchoconstriction.
- Inhibition of mast cell mediator release
- Inhibition of plasma exudation and airway edema
- Increased mucociliary clearance
- Increased mucus secretion
- Decreased cough
- No effect on chronic inflammation Clinical use
- To decrease side effects, they are given by inhalation
- Short acting beta agonists like terbutaline and albuterol act for about six hours. It has faster action, so effective for symptom relief.
- SABAs can be given via a nebuliser or an inhaler
- Drug which act on long acting beta2 receptors for example, formeterol act for around half a day duration. It can be inhaled two times a day

- LABAs when combined with ICS allow reduced dose if ICS to be used

**Side effects**

- Most common are muscle tremor and palpitations common in elderly individuals
- Slight hypokalemia can occur
- Tolerance is a main issue with chronic use ,when beta receptors are downregulated,but bronchodilator effect is not reduced
- But mast rapidly develop tolerance,and this is reduced by simultaneous use of glucocorticoids

**ANTICHOLINERGICS**

- Muscarinic receptor antagonists like ipratropium bromide are useful in preventing cholinergic nerve induced bronchoconstriction and mucus secretion

- As they inhibit only cholinergic pathway they are they are less effective than beta agonists

- High doses can be given via nebuliser but only after beta agonists as they have slower onset of action

- Systemic absorption is minimal,so minimal adverse effects.

## THEOPHYLLINE

- Years before it was given for dilatation of airways orally
- Phosphodiesterases is inhibited in muscle cells, thereby increasing CAMP and causing bronchodilatation.

Clinical use

- Orally given as slow release preparation.
- IV Aminophylline which is a soluble salt of theophylline was initially used for treatment of severe asthma, but now replaced by high dose of inhaled SABAs, as they are more effective with few side effects.
- Now mainly used as an adjunctive therapy

**Side effects**

- Most common side effects are nausea, vomiting,headaches and is due to phosphodiesterase inhibition
- At higher doses, arrhythmias, epiplepsy can occur.
- Adverse effects are directly proportional to plasma concentration and is rarely seen below 10 mg/dl plasma concentration
- Drugs like erythromycin and allopurinol that metabolize cytochrome P450 should be used with caution as theophylline is metabolized in liver by same pathway and so plasma cpncentrations can be elevated[25].
- Enzyme inhibitors like cimetidine congestive cardiac failure,liver disease can lead to decreased clearance of drug

| |
|---|
| **Increased Clearance** |
| • Enzyme induction (rifampicin, phenobarbitone, ethanol) |
| • Smoking (tobacco, marijuana) |
| • High-protein, low-carbohydrate diet |
| • Barbecued meat |
| • Childhood |
| **Decreased Clearance** |
| • Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton, zafirlukast) |
| • Congestive heart failure |
| • Liver disease |
| • Pneumonia |
| • Viral infection and vaccination |
| • High carbohydrate diet |
| • Old age |

**Figure 25 : Factors affecting theophylline clearance**

## CONTROLLER THERAPIES

### Inhaled Corticosteroids

- The most useful controllers for asthma are inhaled corticosteroids, and their early use revolutionized asthma therapy [24].

### Mode of Action

- They are most effective anti inflammatory agents,reducing inflammatory cell number.

- They reduce number of sputum and airway eosinophils,number of mast cells and activated T lymphocytes

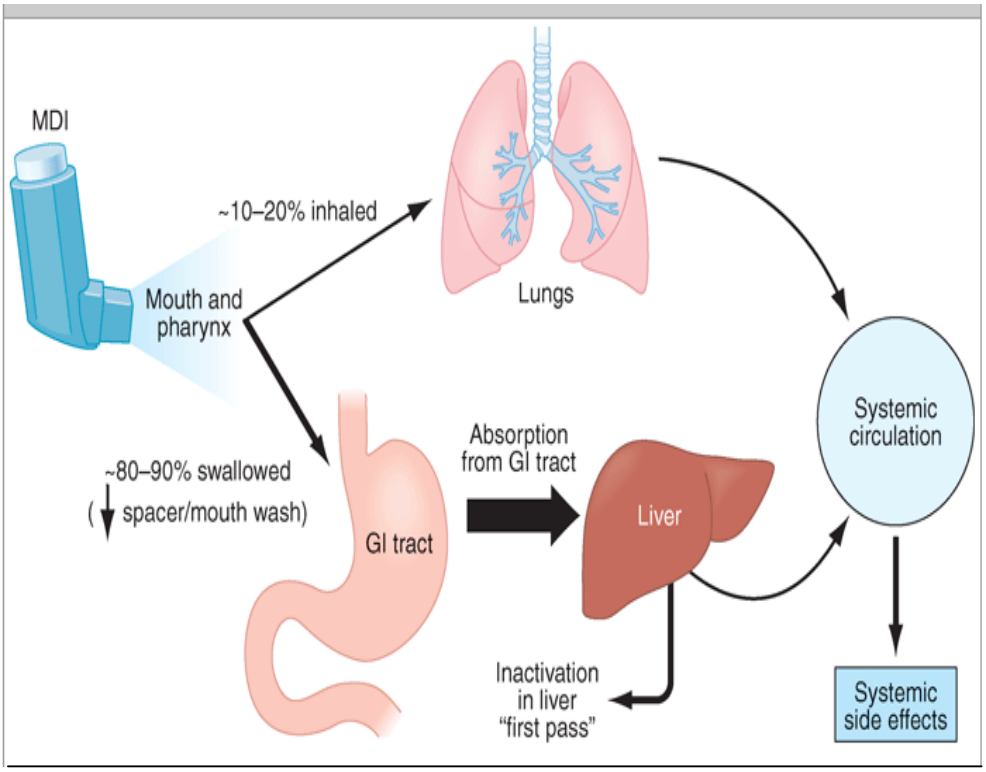



**Figure 26 : pharmacokinetics of inhaled corticosteroids**

## SIDE EFFECTS OF STEROIDS

- Oral candidiasis
- Dysphonia
- At increased doses reduce both plasma and urine cortisol

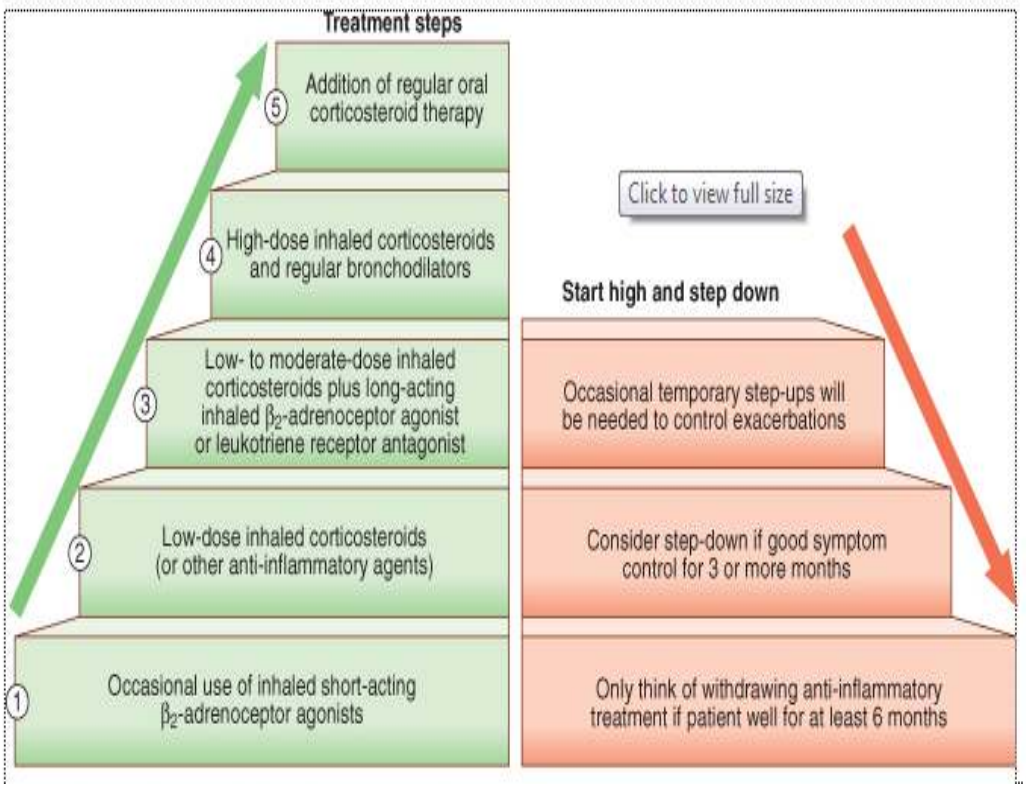



**Figure 27 : Step wise treatment approach**

**Step Wise Treatment Approach**

Step 1-Using inhaled SABAs

Step 2-Introducing ICS in low dose

- To be added in any patient who has developed asthma excacerbation in last 2 yrs
- Uses inhaled beta agonists 3 times/week or more
- Becomes symptomatic 3 times/week or more
- Night awakenings due to asthma once per week

- Starting dose is 400 μg beclometasone dipropionate (BDP) or budesonide(bud)equivalent per day in adults. BDP and BUD are approximately equivalent in clinical practice, although there may be variations with different delivery devices [25].
- Fluticasone and mometasone provide equal clinical activity to BDP/BUD at half the dosage.

**Step 3 –Add on therapy**

- Long-acting $\beta_2$-agonists (LABAs), such as salmeterol and formoterol (duration of action-12 hours) are the first choice

- The first trial put forward the concept of LABA combination with ICS as inhalation therapy was FACET.

- Addition of formeterol to budesonide was more efficous than doubling budesonide dose according to the trial.

- At present, the use of single inhaler therapy as both rescue medication and for controller therapy is propagated by the SMART Approach

- According to SMART[26] approach, Formeterol has a dose response relationship than salmeterol, better bronchodilatation is attained with increasing dose of formeterol than salmeterol.

- Formeterol also has a faster onset of action,is a more dynamic drug than salmeterol and so SMART has a place in GINA guidelines.

- ICS-LABA combinations has undergone a change from FACET to Adjustable maintanence dosing(AMD) to the SMART approach making asthma control goals easy to achieve.

- AMD and SMART suggest a single inhaler therapy for both prevention and relief –AMD following step up combination therapy for few days till control, while SMART suggests combination inhaler therapy for both prevention and relief [26].

- Indacaterol is a once daily LABA, which is newly introduced.

- In future, Mometasone and indacaterol combination if approved could be a milestone in a once daily medication for long term asthma relief.

- Improve asthma control, decrease the frequency and severity of exacerbations when compared to increasing the dose of ICS alone.

**Step 4- Addition of a 4th drug when the response on moderate dose of inhaled steroid and add-on therapy is poor**

- Increase dose of ICS to to 2000 μg BDP/BUD a day

***Step 5: Use of Oral Steroids***

- Oral prednisolone in the lowest dose as a single morning dose can be started[28]

- In patients on long term steroids to prevent osteoporosis,bisphosphonates can be given.

- Steroid-sparing therapies such as methotrexate, cyclosporine, iv gamma globulins can cause significant side-effects.

**Anti-IgE Monoclonal Antibodies**

- Omalizumab rapidly decreases serum IgE and is useful as adjunctive therapy
- Recombinant,humanised monoclonal antibody.
- It binds to portion of Ig E which recognises receptors on surface of mast cells, basophils and dendritic cells. Binding of Ig E to receptors is prevented blocking release.
- Available as sterile, white, reconstituted with water.
- It was recommended by GINA at stage 5, showing moderate results when used as add on therapy either ICS and LABA combination.
- Disadvantage-High cost and less cost benefit ratio.
- Dosage is based on Serum Ig E level and weight of patient. It is given to those having serum Ig E between 30-700 IU/ml, showing sensitisation to air borne allergens like dust mites, moulds, cockroaches.
- Patients are treated for around 5 months for showing positive result without any adverse effect
- No significant side effects
- Anaphylaxis is very rarely seen.

**Anti interleukin 13 therapy**

- IL-13, a cytokine of type 2 helper T cells, involved in asthma development [31].
- Lebrikizumab, newly developed monoclonal antibody to IL-13, binds to it and inhibits its action.

Step-down therapy

When disease is controlled, reducing inhaled /or oral steroid dose should be initiated and maintained at lowest dose at which good control is achieved

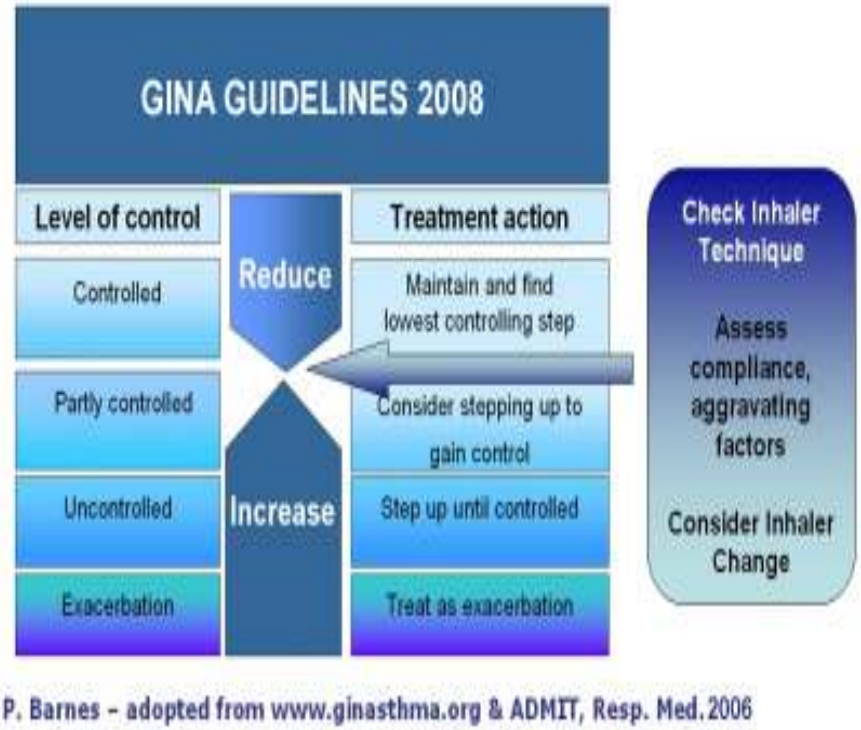



**Figure 28 : GINA Guidelines 2008**

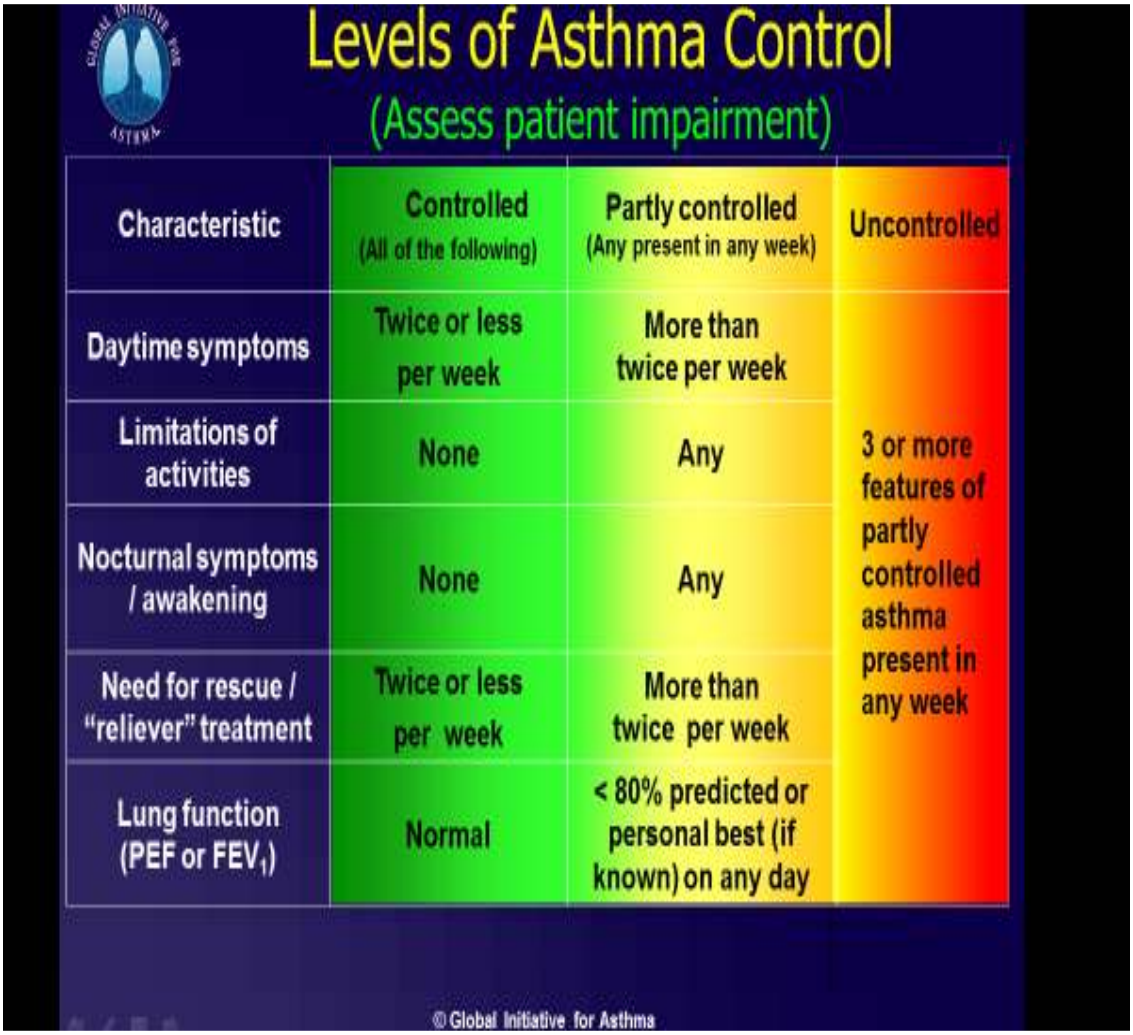



**Figure 29 : Levels of asthma control according to GINA**

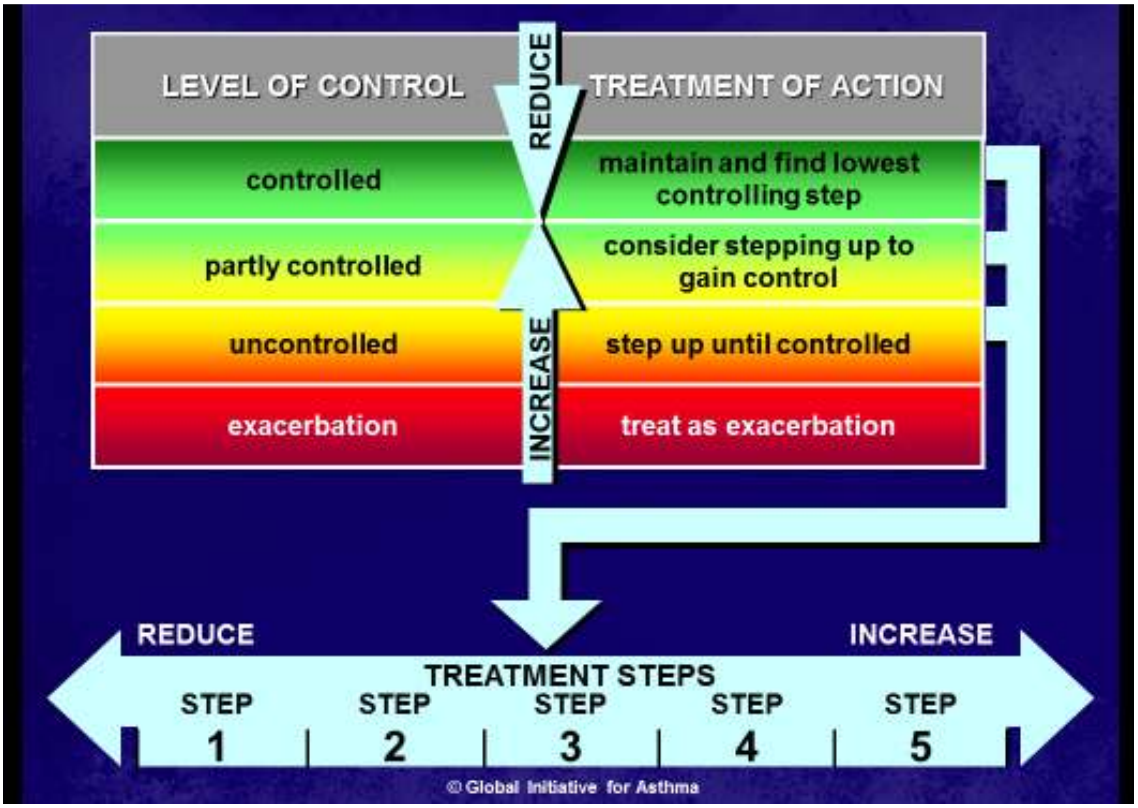



**Figure 30 (a) :Treatment guidelines (GINA)**

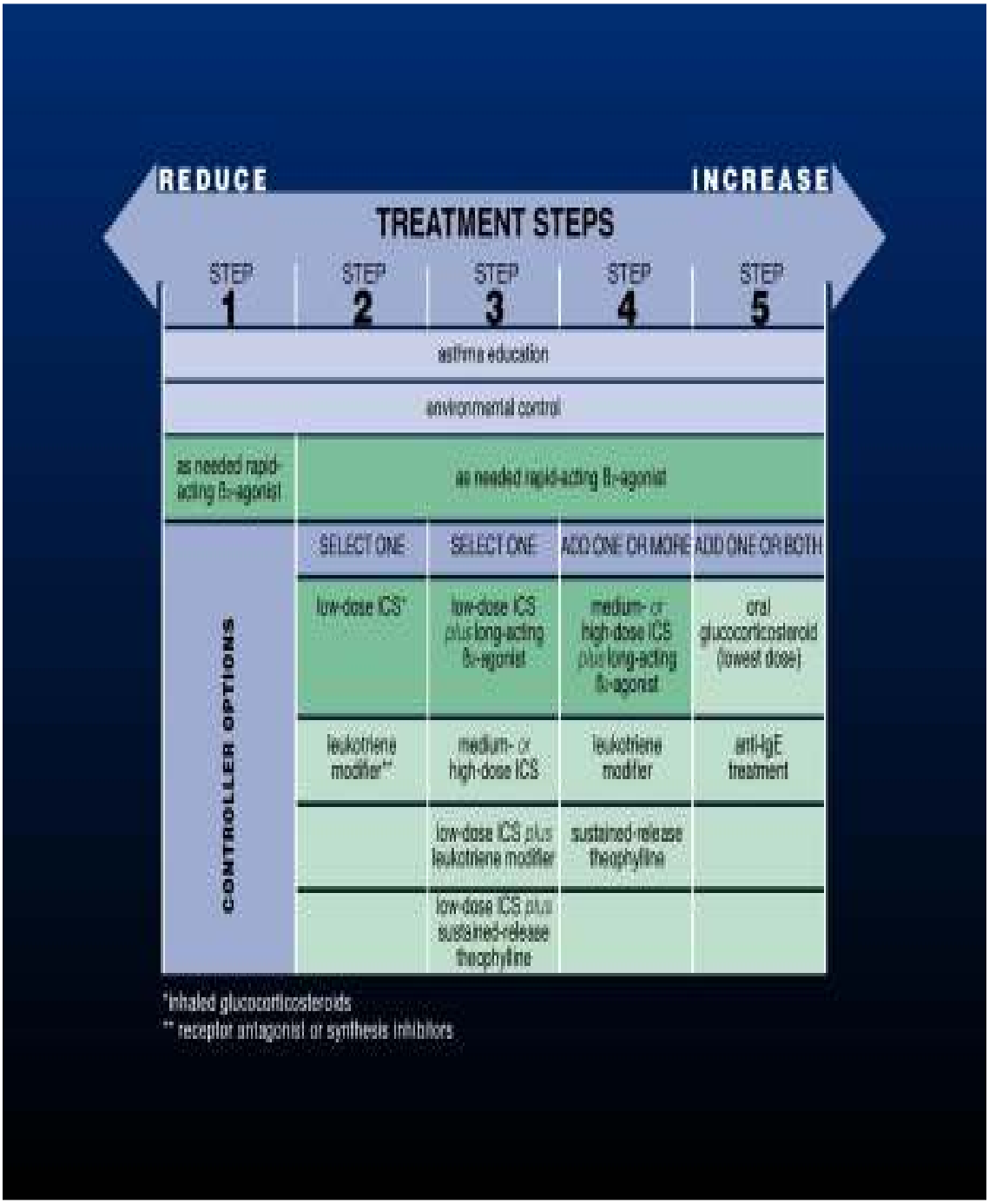



**Figure 30 (b) :Treatment guidelines (GINA)**

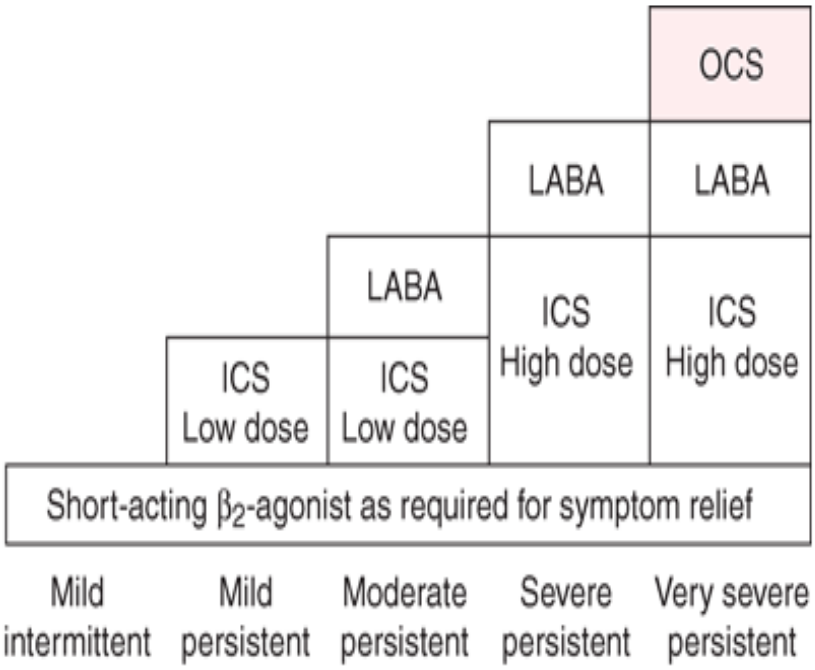



**Figure 31 : Treatment regimen based on severity**

1. Mild Intermittent Asthma[29]

- Inhaled beta agonists usually provide relief

2. Mild Persistent Asthma

- Low-dose inhaled glucocorticoids are the preferred medications.
- Leukotriene inhibitors, cromolyn, or nedocromil are alternatives

3.Moderate Persistent Asthma

- Low-dose inhaled steroidscombined with a long acting beta agonist or medium-dose inhaled steroids is the preferred therapy

**4. Severe persistent asthma**

- Asthma in which symptoms persist ,despite treatment with high-dose inhaled glucocorticoids and additional therapy with long-acting beta agonists, leukotriene pathway inhibitors, or theophylline.

- Poor drug compliance or exposure to environmental factors or drugs such as aspirin or beta blockers are frequent causes.So detailed probe into these factors is indicated before the start of additional drug therapy.

- Options include

  a) Increasing the dose of inhaled glucocorticoids

  b) Adding sustained-release theophylline or a leukotriene modifier in patients already taking inhaled glucocorticoids and LABAs[30]

  c) adding a LABA to the regimen for patients already taking inhaled steroids and theophylline or a leukotriene modifier

  d) Anti IgE antibody omalizumab has been shown to be useful

| Asthma Severity* | Mild* | Moderate* | Severe* |
|---|---|---|---|
| Daytime symptoms | 2–6 days/week<br>Usually no reduction in activity | Daily<br>Exacerbations reduce activity | Continual<br>Significant reduction in activity |
| Nocturnal awakenings | More than two monthly | More than once weekly | Most nights |
| Relief medication use | Less than daily | Daily | Several times daily |
| Lung function $FEV_1$ | >80% Predicted | 60–80% Predicted | <60% Predicted |
| PEE variability | <30% | >30% | >30% |
| Controller medications | Low-dose ICS (highly preferred)<br>OR<br>Leukotriene receptor antagonist<br>OR<br>Theophylline SR | Low–moderate dose ICS + long acting β-agonist<br>OR<br>Low–moderate dose ICS + Leukotriene receptor antagonist<br>OR<br>Low–moderate dose ICS + theophylline SR | Moderate–high dose ICS + long acting β-agonist<br>AND<br>Oral steroids<br>Anti-IgE therapy |
| Relief medications | Short-acting MDI | Short-acting MDI | Short acting MDI<br>Consider HFN |
| Diagnose and treat other conditions | Manage environment | Manage environment | Manage environment |
| | Treat rhinosinusitis | Treat rhinosinusitis<br>Assess for GERD with esophageal pH study | Treat rhinosinusitis<br>Assess for GERD with esophageal pH study |
| Written action plans | Consider | Recommended, base on $PEF/FEV_1$ | Recommended, base on $PEF/FEV_1$ |
| Immunotherapy | Consider | Consider | Contraindicated |
| Monitoring | Annual spirometry | Annual office spirometry<br>Monitor PEF<br>Consider home spirometry | Annual office spirometry<br>Monitor PEF<br>Consider home spirometry |

**Figure 32 : Symptomatology,spirometry results and management based on severity.**

## Immunotherapy in asthma

- Allergen immunotherapy is found to be useful in selected patients with defined allergic triggers. Generally, patients having many allergic triggers benefit less from immunotherapy than those having identified with a single trigger.

- Patients with mild or moderate persistent asthma who arenot adequately controlled with inhaled drugs can beconsidered for immunotherapy.

- Those with concomitantnasal symptoms are benefitted the most.
- Although serious complications from immunotherapy are rare, they occurmore frequently in patients with asthma.
- Incidence of adverse systemic reactions is very high, so patients whose FEV1 is less than 70 percent of predicted should be considered at high risk of complications from immunotherapy

**Treatment of Associated Conditions**

- Effective asthma treatment of asthma needs treatment of conditions that lead to aggravation of asthmatic symptoms [31] .

- Asthma can coexist with many disorders that affect lung function.

- Gastroesophageal reflux disease, obesity, and chronic sinusitis are the most commonly associated with poor control of asthma

**Other Considerations**

- For acute asthma exacerbations, unless there is objective evidence of bacterial pneumonia or co-existing bacterial sinusitis, antibiotics are not indicated.

- Oxygen therapy is needed to avoid hypoxia -oxygen saturation greater than or equal to 92 percent is to be maintained.

- Oxygen should be titrated to the lowest dose needed as excessive oxygen concentrations can lead to CO2 retention and a respiratory acidosis in some patients [31].

- Deep venous thrombosis is indicated for the hospitalized asthma patient.

- As there is increased use of steroids, stress ulcer prophylaxis is also indicated.

**Special situations**

**1.Asthma in Elderly**

- Side effects more common due to therapy like muscle tremor with beta agonists and increased systemic side effects with ICS.
- Interactions with drugs and comorbidities frequent.
- Chronic obstructive pulmonary disease may coexist

- OCS trial may be beneficial in documenting steroid responsiveness.

**2. Pregnancy and asthma**

- 1/3rd of asthmatics improve, 1/3 rd worsen and 1/3 rd remain same.
- SABAs, ICS, and theophylline are safe.
- Prednisone better than prednisolone as it cannot be converted to active prednisolone by fetal liver.
- Breast feeding is not contraindicated when on drugs.

**3. Smoking and asthma**

- Smoking affects anti-inflammatory action of steroids thereby increasing requirement for higher dose.
- Vigorous smoking cessation should be followed

**4. Surgery and asthma**

- Adrenal suppression can occur in OCS treated patients and so increased dose of OCS prior to surgery is needed.
- Poor wound healing and increased infection due to high dose of corticosteroid use may be a contraindication to surgery.

# MATERIALS AND METHODS

## Source of data

The study was conducted among patients who presented to Coimbatore medical college medicine outpatient/pulmonary medicine outpatient department / those who got admitted in Coimbatore medical college hospital.

## Sample size

100

## Study period

From August 2013 to August 2014.

## Study design

Observational clinical study

## Study population

Hundred patients who presented initially with wheeze and breathlessness were included in the study.

## Inclusion criteria

- Age group 18-60 years
- Clinical features of bronchial asthma as per GINA Guidelines.
- All cases of Bronchial Asthma of age group 18-60 years having proven airflow reversibility by Spirometry.

- Patients willing to give written informed consent to participate in the study.

**Exclusion Criteria**

- Patients having on going or past history of tuberculosis ,chronic obstructive pulmonary disease or interstitial lung disease.
- Any history of haemoptysis.
- Those on oral corticosteroids prior to the study.
- Congestive cardiac failure patients.
- Evidence of infective exacerbation like fever, purulent expectoration, raised leukocyte counts, specific growth of micro-organisms in sputum culture.
- Pregnant females with asthma

**METHODOLOGY**

- Patients who attended hospital with complaints of wheeze and breathlessness,and associated symptoms like cough and nocturnal awakenings were included for the study.
- Symptomatology and duration was recorded for all.
- Spirometry was done and FEV1 and PEF was measured both before and twenty minutes post nebulisation withsalbutamol..

- Asthma severity was analysed by both history and prebronchodilator FEV1% of Predicted .
- According to latest GINA Guidelines,severity was also assessed as follows

1. Controlled asthma –No day time symptoms(less than twice/week),No limitation of activities,No nocturnal symptoms or awakening,No need for rescue or reliever treatment(less than twice/week),Normal lung function tests, No excacerbations.

2. Partially controlled asthma- More than twice/week day time Symptoms, any limitation of activities, any nocturnal awakenings,reliever or rescue treatment more than twice/week.

3. Uncontrolled asthma-3 or more features of partly controlled asthma present in any week,one in any week excacerbation.

Method of data collection

- **Serum Ig E**

Venous clotted blood of 2 ml was used for measuring IgE levels using commercially available diagnostic ELISA kits.It is a solid phase enzyme linked immunosorbent assay based on sandwitch technique.

- **Absolute eosinophil Count**

Venous EDTA blood will be subjected to automated analyser for AEC and confirmed by peripheral smear.

**STATISTICAL ANALYSIS**

All the information obtained from our study population was collected and recorded in master chart. Statistical significance was analysed by Chi-square test and logistic regression analysis was performed with SPSS software to assess independent association of variables found to be significant in univariate analysis.

**Concept of P value**

- If the P value is between **0.000 to 0.010**, it is considered to be significant at level 1- **Highly Significant**

- If the P value is between **0.011to 0.050,**it is considered to be significant at level 5- **Significant**

- If the P value is between **0.051-1.000**,it is considered insignificant

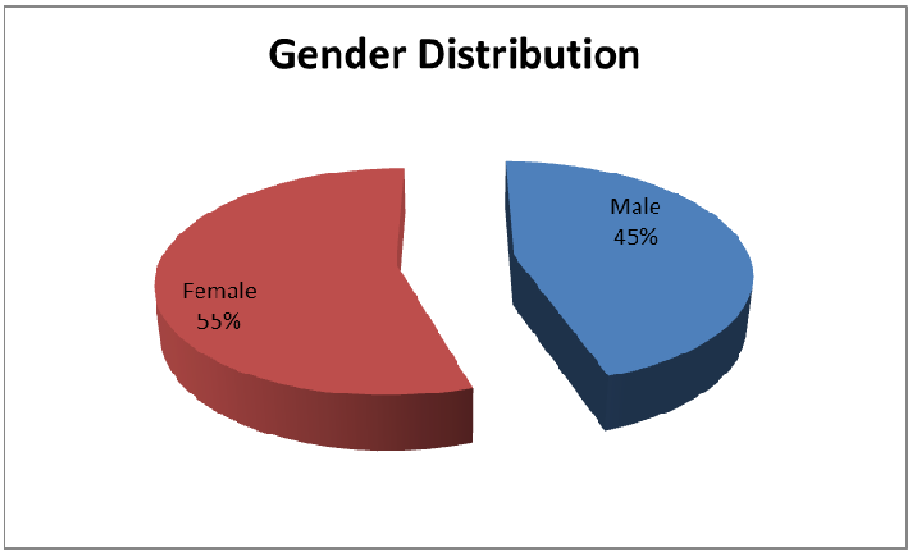
At level 5 -**Not Significant**

# OBSERVATION AND ANALYSIS

## TABLE 1.SEX DISTRIBUTION OF STUDY POPULATION

| SEX | PERCENT |
|---|---|
| Male | 45 |
| Female | 55 |
| Total | 100 |

## CHART 1. SEX DISTRIBUTION OF STUDY POPULATION

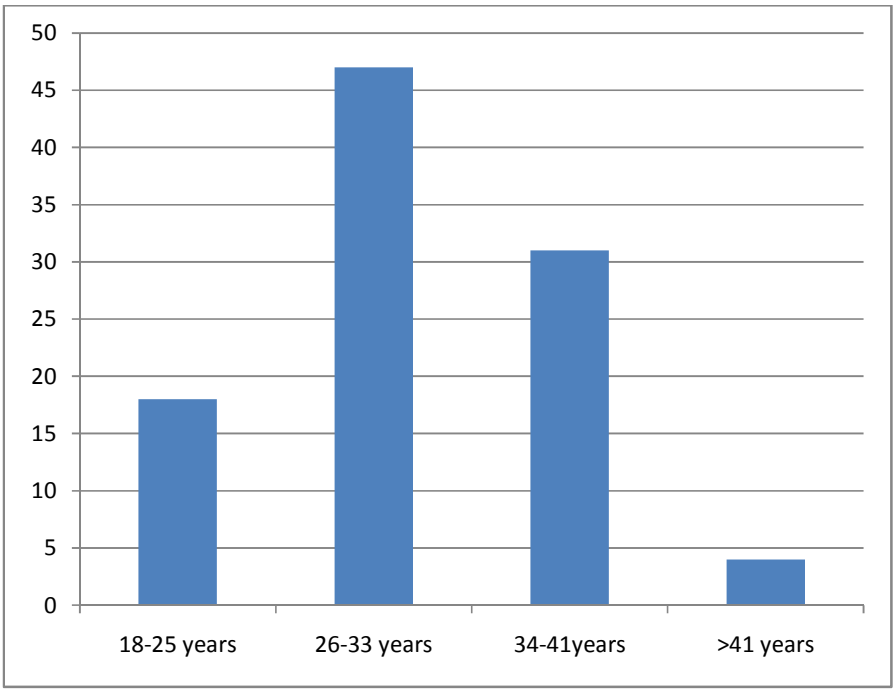



In our study, the male to female ratio was 1:1.2 with males constituting 45% and females constituting 55% of bronchial asthma cases.

## TABLE 2. AGE DISTRIBUTION OF STUDY POPULATION

| AGE(YEARS) | PERCENTAGE |
|---|---|
| 18-25 | 18 |
| 26-33 | 47 |
| 34-41 | 31 |
| >41 | 4 |
| TOTAL | 100 |

## CHART 2. AGE DISTRIBUTION OF STUDY POPULATION

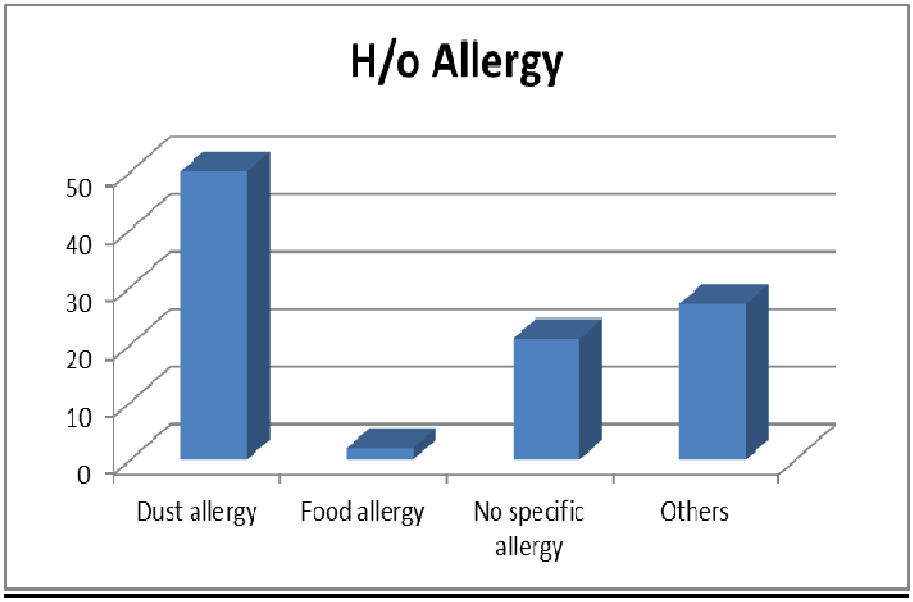



**Most common age group in our study population was 26-33 years**

## TABLE 3. INCIDENCE OF ALLERGY

| ALLERGY | FREQUENCY | PERCENTAGE |
|---|---|---|
| DUST ALLERGY | 50 | 50 |
| FOOD ALLERGY | 2 | 2 |
| OTHERS | 27 | 27 |
| NO SPECIFIC ALLERGY | 21 | 21 |
| TOTAL | 100 | 100 |

## CHART 3. INCIDENCE OF ALLERGY

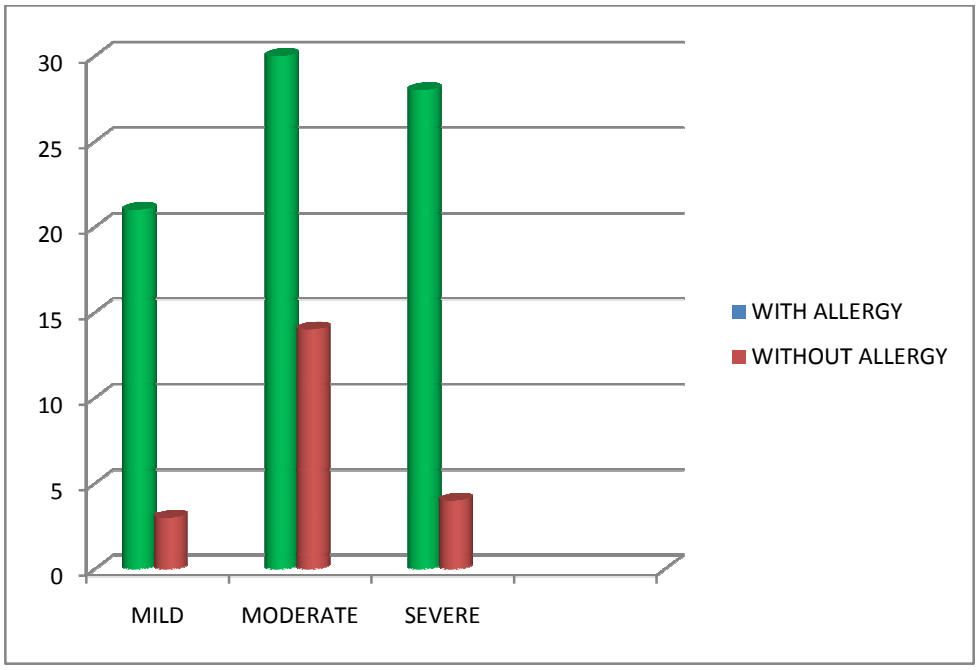



**Among 100 cases of bronchial asthma in this study, 79 had history of some allergy to dust or food or others.**

## TABLE 4. ALLERGY AND PREVALENCE

| | MILD | MODERATE | SEVERE | |
|---|---|---|---|---|
| WITH ALLERGY | 21 | 30 | 28 | P Value 0.002 |
| WITHOUT ALLERGY | 3 | 14 | 4 | |
| TOTAL | 24 | 44 | 32 | Highly significant |

## CHART 4. ALLERGY AND PREVALENCE

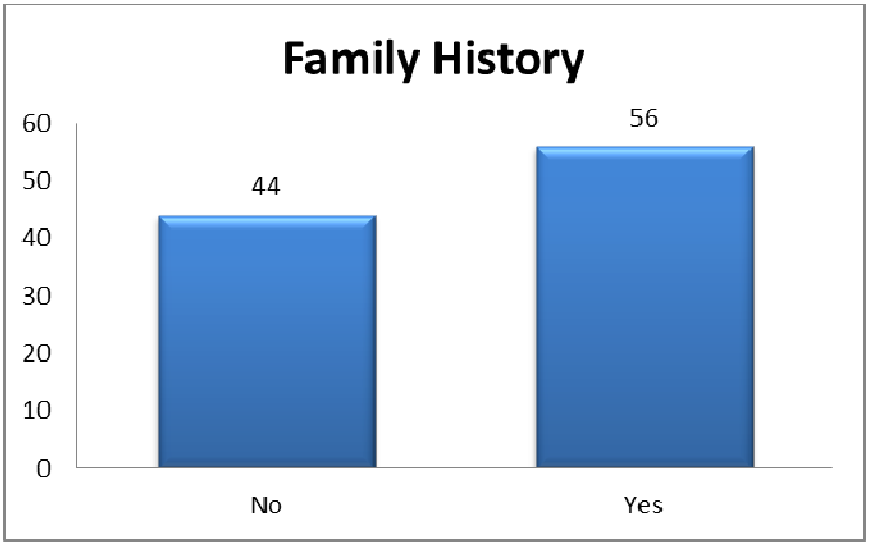



**Prevalence of asthma is more in patients with allergy in our study population.**

**TABLE 5. INCIDENCE OF FAMILY HISTORY**

| INCIDENCE | YES | NO |
|---|---|---|
| PERCENTAGE | 56 | 44 |

**CHART 5. INCIDENCE OF FAMILY HISTORY**

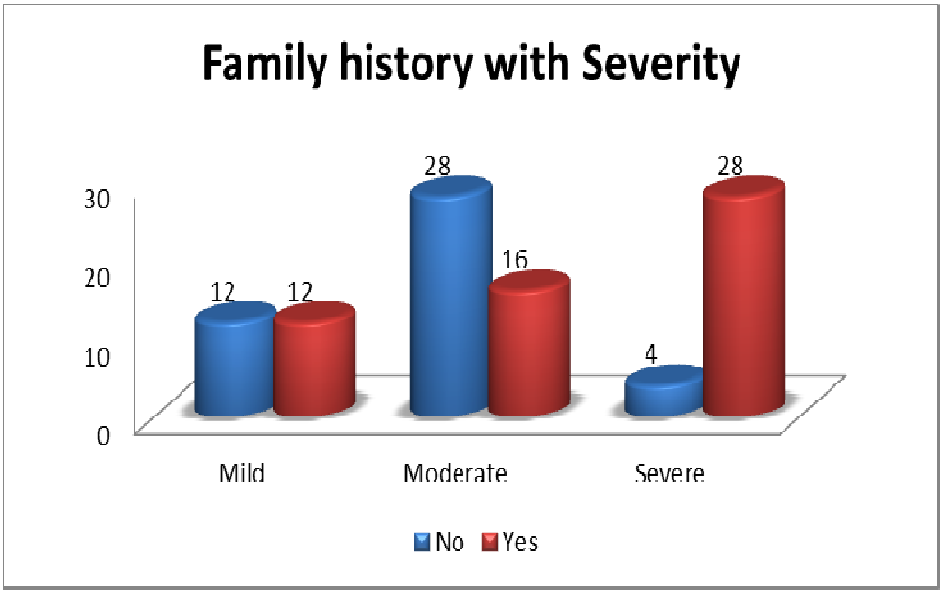



**Family history was positive in 56% of cases in our study.**

## TABLE 6. FAMILY HISTORY AND SEVERITY OF ASTHMA

| | MILD | MODERATE | SEVERE | |
|---|---|---|---|---|
| YES | 12 | 16 | 28 | P Value 0.001 |
| NO | 12 | 28 | 4 | |
| TOTAL | 24 | 44 | 32 | |

## CHART 6. FAMILY HISTORY AND SEVERITY OF ASTHMA



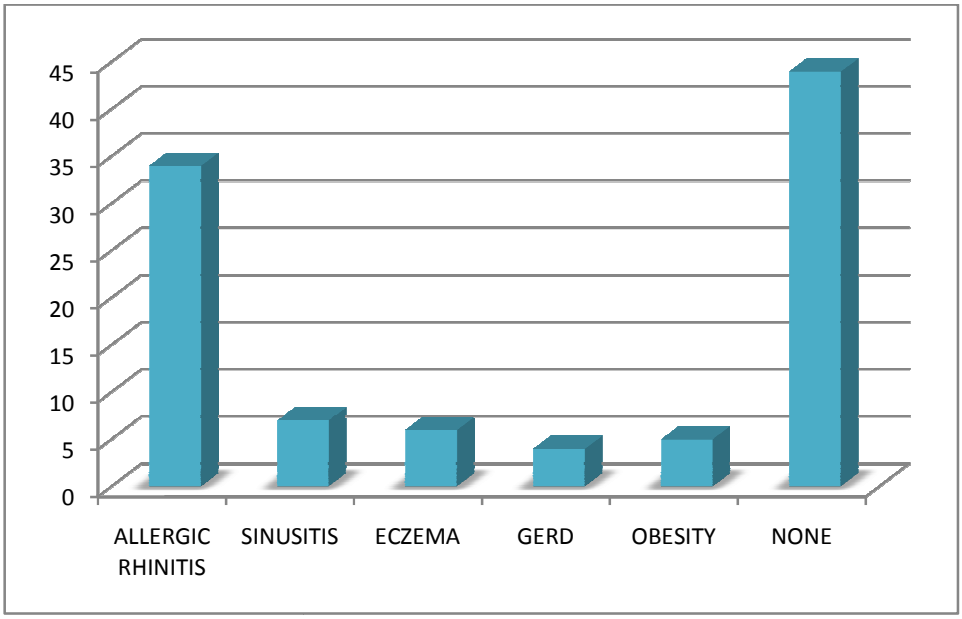

- In our study population,56% had a positive family history

- Among the 56% who had a positive family history,28% had severe, 16% had moderate and 12% had mild asthma.P value was 0.0001.

## TABLE 7 .ASSOCIATION OF ASTHMA WITH VARIOUS CO MORBID CONDITIONS

| COMORBID CONDITIONS | PERCENTAGE |
|---|---|
| ALLERGIC RHINITIS | 34 |
| SINUSITIS | 7 |
| ECZEMA | 6 |
| GERD | 4 |
| OBESITY | 5 |
| NONE | 44 |
| TOTAL | 100 |

## CHART 7. ASSOCIATION OF ASTHMA WITH VARIOUS COMORBID CONDITIONS




**Allergic rhinitis was the most common co morbid condition associated with bronchial asthma in our study.**

## TABLE 8 : COMORBID CONDITIONS AND SEVERITY

| | No.of cases | Mild | Moderate | Severe | |
|---|---|---|---|---|---|
| With comorbid conditions | 56 | 11 | 23 | 22 | P VALUE 0.002 |
| Without comorbid conditions | 44 | 13 | 21 | 10 | |
| Total | 100 | 24 | 44 | 32 | |

## CHART 8 : COMORBID CONDITIONS AND SEVERITY

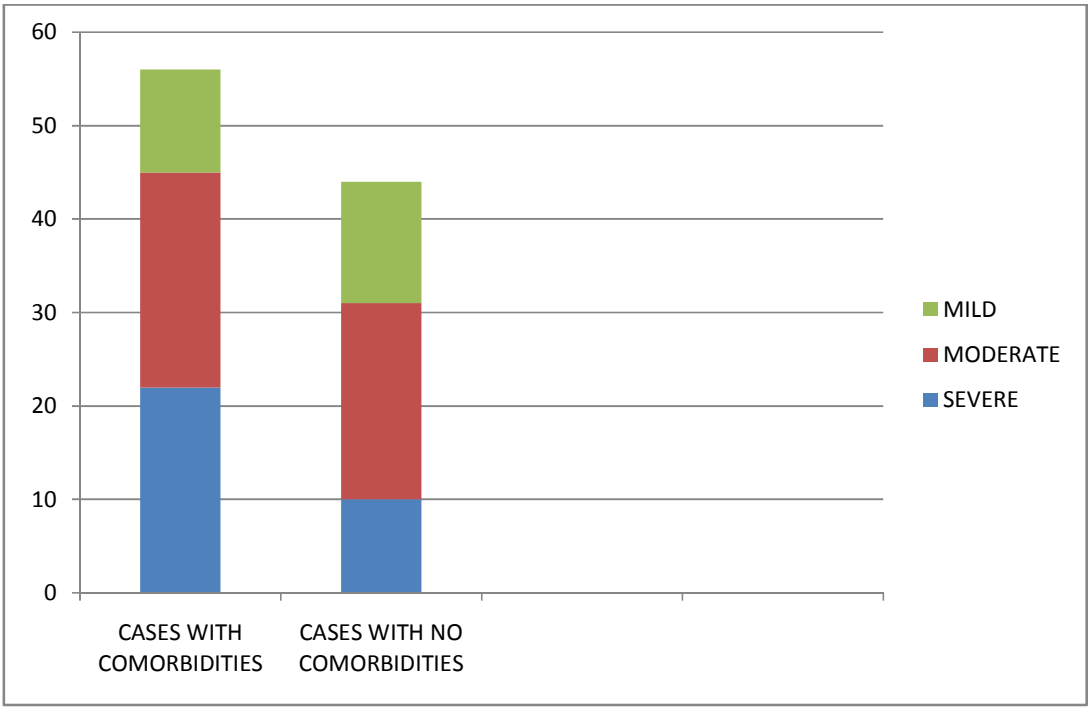
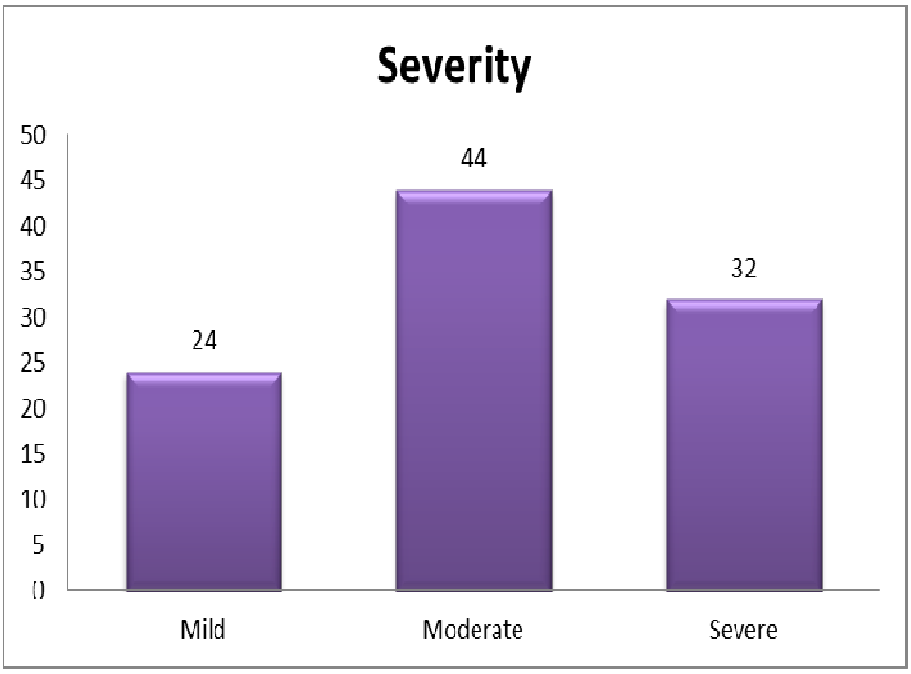


**TABLE 9. SEVERITY ASSESSED BY LUNG SPIROMETRY**

| SEVERITY | FREQUENCY | PERCENTAGE |
|---|---|---|
| Mild | 24 | 24 |
| Moderate | 44 | 44 |
| Severe | 32 | 32 |
| Total | 100 | 100 |

**CHART 9. SEVERITY ASSESSED BY LUNG SPIROMETRY**

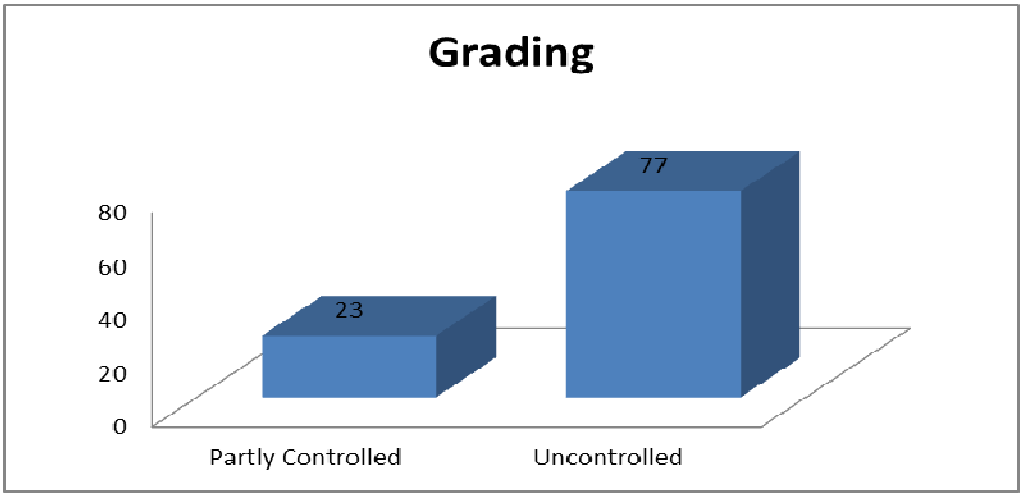



**Asthma severity based on spirometry is classified as intermittent and mild persistent with FEV1≥80% P, moderate persistent with FEV160-80% P,and severe persistent with ≤ 60%P. In our study,44% cases were moderate and 32% wassevere.**

**TABLE 10 : SEVERITY ACCORDING TO NEW GINA GUIDELINES**

| SEVERITY | PERCENTAGE |
|---|---|
| PARTLY CONTROLLED | 23 |
| UNCONTROLLED | 77 |

**CHART 10 : SEVERITY ACCORDING TO NEW GINA GUIDELINES**




**According to latest GINA guidelines,the severity of our cases were 77% uncontrolled and 23% partially controlled.**

**TABLE 11 : ABSOLUTE EOSINOPHIL COUNT AND SEVERITY OF ASTHMA**

| Absolute eosinophil count(cells/cu.mm) | MILD | MODERATE | SEVERE | P VALUE 0.001 |
|---|---|---|---|---|
| Upto 440 | 24 | 40 | 12 | |
| >440 | 0 | 4 | 20 | |

**CHART 11 : ABSOLUTE EOSINOPHIL COUNT AND SEVERITY OF ASTHMA**

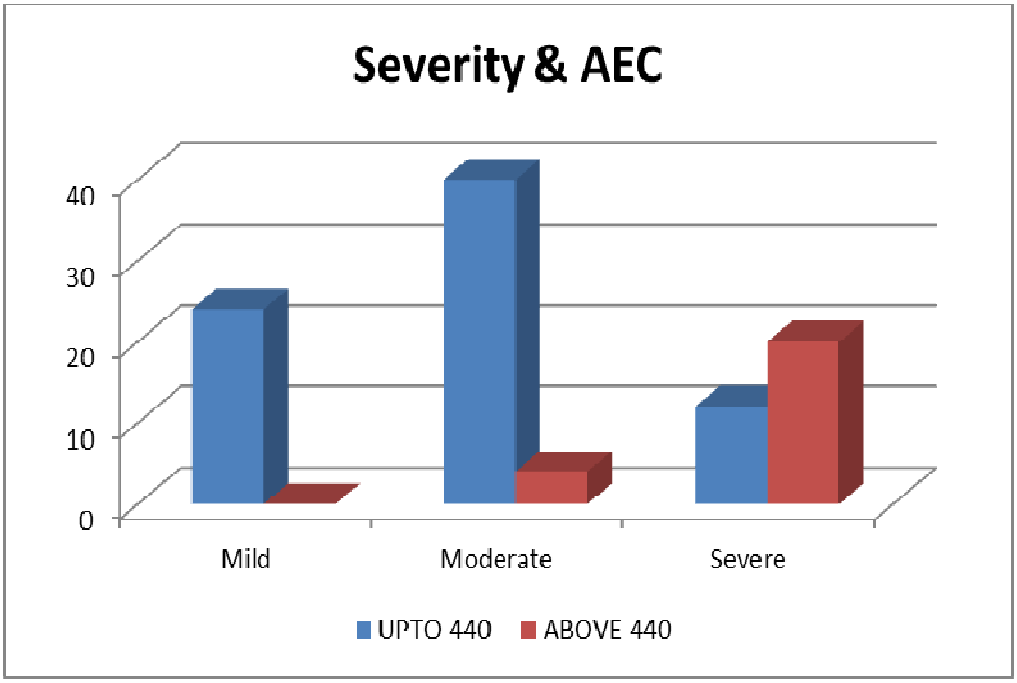
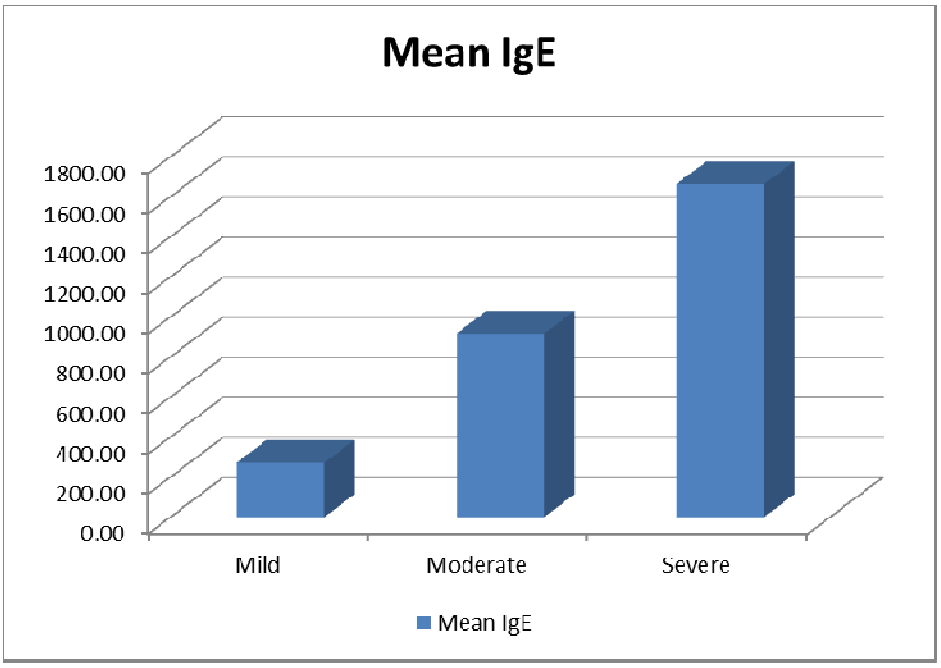


**TABLE 12. MEAN SERUM IgE AND SEVERITY**

| SEVERITY | Mean IgE(IU/ml) |
|---|---|
| **MILD** | 271.50 |
| **MODERATE** | 916.48 |
| **SEVERE** | 1662.59 |

**CHART 12 : MEAN SERUM IgE AND SEVERITY**

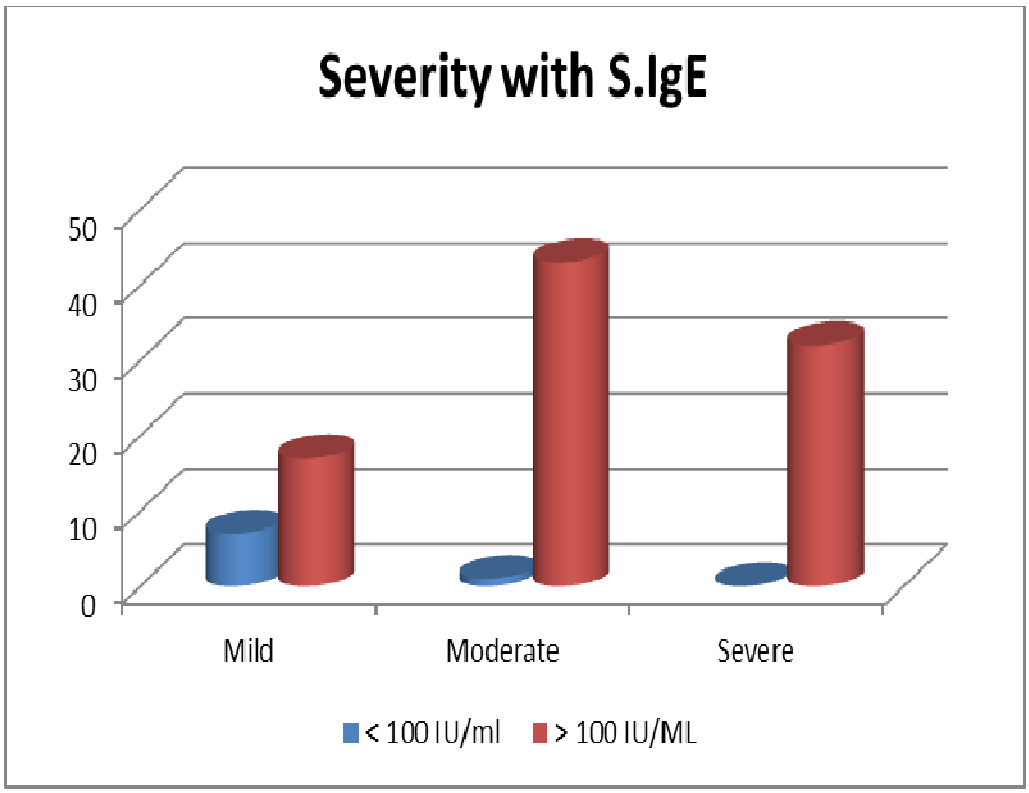



**Mean Ig E in the mild asthma patients was 271.50 IU/mL,in the moderate asthma group was 916.48IU/mL,and in the severe group was 1662.59 IU/ml.**

**TABLE 13 : SERUM Ig E LEVELS AND SEVERITY**

| Serum IgE(IU/ml) | MILD | MODERATE | SEVERE | P VALUE 0.001 |
|---|---|---|---|---|
| < 100 | 7 | 1 | 0 | |
| >100 | 17 | 43 | 32 | |

**CHART 13 : SERUM Ig E LEVELS AND SEVERITY**



# RESULTS

- In our study common age group with bronchial asthma was 26-30 years
- Female sex predilection was seen in adults, with male to female ratio of 1:1.2
- In our study population,79%had history of allergy to dust,food or others and 21% had no history of allergy
- 56% of study population had associated comorbid conditions.
- Among the associated comorbid conditions, 34% had allergic rhinitis, 7% had sinusitis, 6%had eczema, 4%had GERD,5% had obesity.
- Allergic rhinitis was the most common assossiated co morbid condition.
- Severity of asthma had positive correlation with the occurance of co morbidities**.** (P Value 0.002)
- In our study population,56% had a positive family history
- Among the 56% who had a positive family history,28% had severe, 16% had moderate and 12% had mild asthma.P value was 0.000
- Mean AEC in our study population was 423.08 cells/cu.mm.
- Among the 32% severe cases of bronchial asthma in the study, 20% had absolute eosinophil counts >440 cells/cu.mm, with P Value 0.000 showing high significance.
- Among the moderate persistent group only 4% had AEC >440 cells/cumm & in the mild persistent group none had AEC > 440cells/cu.mm.
- Among the 100 cases of bronchial asthma studied,mean Ig E in the mild asthma patients was 271.50 IU/mL, in the moderate asthma group was 916.48IU/mL, and in the severe group was 1662.59 IU/mL.

- Among the 24 mild asthmatic patients, 17% had S.IgE >100 IU/mL and among the 44% moderate persistent patients, 43% had S.IgE >100 IU/mL and 32% severe cases, all had S.Ig E >100 IU/mL .

- P Value was 0.000 showing high statistical significance between S.Ig E level and severity of asthma.

# DISCUSSION

In this section, we are comparing the results of our study with previous studies conducted and their results .This was a study conducted in Coimbatore medical college hospital with 100 consecutive patients. The purpose of the study was to find out if there was any correlation between absolute eosinophil count, serum Ig E levels and severity of bronchial asthma also evaluated the patients for symptoms,risk factors, family history,and comorbid conditions to assess its relation with asthma severity.

**TABLE : 14**
**COMPARING SEX DISTRIBUTION WITH OTHER STUDIES**

| **STUDY** | SEX |
|---|---|
| **PRESENT STUDY** | **F >M** |
| B.LEYNAERT ET AL | F >M |
| D.MARCO ET AL | F >M |
| BAPNA ET AL | F>M |

- B.Leynaert et al studies have shown that asthma was 20% more frequent in females than in males over the age of 35 years. Incidence of nonallergic asthma was higher in females than in men throughout all reproductive age group.

- Bapna et al in 1998 reported that female sex show higher predilection than males
- Studies done by Kynyk Et al show that women are more likely to develop asthma and suffer from more mortality than men.Hormonal and genetic susceptibility both contribute to this change.
- Studies by de Marco.R et al also show severe asthma is more predominant in women.During childhood, girls had a significantly lower risk of developing asthma than boys (relative risk (RR): 0.74 and 0.56 in the 0 to 5yr and 5 to 10 yr age, respectively). Around puberty, the risk was almost equal in the two sexes (RR = 0.84). After puberty, the risk in women was always significantly higher than that in men (RR: 1.38 to 5.91). This pattern was consistent in all 16 countries studied from 1991 to 1993 . Women's greater susceptibility to asthma in early adulthood was at least partly, explained by their smaller airway calibre.

**ALLERGY AND ASTHMA SEVERITY**

- Prevalence of asthma is more in patients with allergy in our study population.
- According to studies by Lebowitz et al and Peat et al, the role played by atopy contributes to the highest risk.

## FAMILY HISTORY AND ASTHMA SEVERITY

- In our study population,56% had a positive family history. Among the 56% who had a positive family history,28% had severe,16% had moderate and 12% had mild asthma.
- P value was 0.001 showing high statistical significance.
- Results of a study done by Parisa Davoodi,P.A Mahesh,and Nallur B.Ramachandra indicated a positive association between having a family history of asthma and higher socio-economic status. Family history of asthma and a topy have been introduced as the strongest risk factors in adult asthma

**TABLE : 15**
**COMPARING FAMILY HISTORY AND ASTHMA SEVERITY WITH OTHER STUDIES**

| **PRESENT STUDY** | PERCENTAGE |
|---|---|
| PRESENT STUDY | 56% |
| PARISA DAVOODI et al | 61% |

## ASTHMA AND ASSOCIATED COMORBIDITIES

- In our study, 56% had associated comorbidities of which allergic rhinitis constituted 34 cases, others were sinusitis, eczema, obesity and GERD. Comorbidities had positive correlation with severity of bronchial asthma as assessed by spirometry which were similar to studies by de Groot et al and Andrea G Gershon

- Studies by Louis Philippe Boulet,Marie Eve Boulay ,report that asthma in adults is most commonly associated with comorbidities such as rhinitis, sinusitis, obesity, obstructive sleep apnea and gastro-oesophageal reflux disease which is similar to comorbidities in our study population.

- In a study done by de Groot et al ,the comorbidity associated with AR is high in adult age group and in children

- In a study done to assess the burden of co morbidities in asthma individuals by Andrea S Gershon, Teresa To, Jun Guan in Ontario,Canada among 12 million residents,obesity,depression and allergic rhinitis were associated co morbidities.

- Soriano *et al*. estimated the prevalence of comorbid diseases from an administrative data-based study including **7931** patients with asthma and matched controls.The most prevalent associated condition in adult asthmatic patients was time-limited minor infections while others with a high impact and/or high prevalence were depression, hypertension, diabetes, ischemic heart disease, degenerative joint disease, cardiac arrhythmia,and COPD. A total of 60% of adult asthma patients had at least one condition, and 12% had three or more

**TABLE : 16**
**COMPARING ASSOCIATED COMORDITIES WITH OTHER STUDIES**

| STUDY | ASSOCIATED COMORDITIES | PERCENTAGE | CORRELATION WITH SEVERITY |
|---|---|---|---|
| Present Study | Allergic rhinitis ,Obesity, Sinusitis, Eczema, GERD | 56 | Positive |
| Soriano et al | Allergic Rhinitis, Hypertension, Ischemic heart disease, Depression | 60 | Positive |
| deGroot et al | Allergic Rhinitis | 51 | Positive |
| Andrea S Gershon | Allergic Rhinitis | 54 | Positive |

**TABLE : 17**

**COMPARING MEAN SERUM Ig E AND SEVERITY WITH OTHER STUDIES**

| STUDY | MEAN Ig E ( IU/ml) | | | P VALUE |
|---|---|---|---|---|
| | MILD | MODERATE | SEVERE | |
| PRESENT STUDY | 271.50 | 916.48 | 1662.59 | 0.000 |
| SRIKANTAIAH ET AL | 250 | 846 | 1045.32 | |
| JANEWAY ET AL | 304.6 | 882.4 | 1420.48 | |

Among the 24 mild asthmatic patients, 17 % had S.IgE >100(IU/Ml) and among the 44% moderate persistent asthma patients,43% had S.IgE >100 ( IU/ml)and 32% severe cases, all had S.Ig E >100.Severity of asthma statistically correlates with the serum level of Ig E.

- Our present study shows that suggest that S. IgE levels increase with severity which is similar to studies by Janeway et al and Kovac et al.

- Burrow et al in 1982 and Castorline et al in 1983 first described role of S.Ig E and air flow obstruction in asthma

- In our study, mean serum Ig E in mild, moderate and severepersistent cases was 271.50, 916 48, 1662.59 which is similar to the study by Srikantaiah et al

- Studies done by Kornelija Kovac et al in children aged 5-15 years showed that asthmatic children have elevated S.IgE concentration. Asthmatic children with higher asthma severity have a higher concentration of both Total Ig E (>288 IU/mL) and specific Ig E to Dermatophagoides pteronyssinus (>44.1IU/ml)

**TABLE : 18**

**COMPARING ABSOLUTE EOSINOPHIL COUNT (AEC) AND SEVERITY OF ASTHMA WITH OTHER STUDIES**

| STUDY | MEAN AEC (cells/cu.mm) | CORRELATION WITH SEVERITY |
|---|---|---|
| PRESENT STUDY | 423.08 | P VALUE O.OO1 Positive |
| MILAAT ET AL | 581.7 | Positive |
| KOSHAK ET AL | 480.28 | Positive |

- In our study among the 32 severe asthma patients, 20 had raised AEC with high statistical significance similar to the study by Koshak et al and Kamfar et al.

- In a study done by Koshak et al ,60 asthmatics aged 15 to 70 years, of which 68.3% were female, were studied. Severity levels differed between the two assessment methods in 45% of the cases and showed a predominance of the moderate persistent type. Absolute eosinophil count ranged between 22 and 2470 cells/mm3 and eosinophilia was found in 50% of the cases. AEC showed a high positive correlation with increased asthma severity level assessed by history alone.

- In a study by Kamfar HZ ,Milaat et al,i n asthma patients,the AEC for the groups ranged between 10 and 2100 cells/mm3 (mean = 581.7 cells) and showed a very significant positive correlation with increased asthma severity ( $p<0.001$). A high linear trend of AEC within each clinical group was found ( $p<0.0001$), and the means among each group also showed a significant increase as asthma severity level increased ( $p<0.001$). The study documents a significant positive correlation between the clinical severity of bronchial asthma and eosinophil counts. Authors advocate the use of this simple and sensitive laboratory test as significant adjunct objective technique in the assessment of asthma severity and management.

# SUMMARY


- This present study is an observational clinical study which analysed the correlation of serum immunoglobulin E levels and absolute eosinophil count with the severity of bronchial asthma.
- Study was conducted during a period of one year from August 2013 to August 2014. It involved 100 patients which were randomly selected from among outpatients and inpatients presenting to Coimbatore medical college hospital.
- Relevant history and physical findings including symptoms were recorded.
- Routine haematological, biochemical investigations, Chest X ray were done.
- Spirometry was done in all patients and FEV1 and PEF was measured both before and 20 minutes after giving nebulised salbutamol. Post bronchodilator reversibility of 12% or more was taken as criteria for diagnosis of asthma.
- Severity of asthma was assessed by both history and prebronchodilator FEV1% Predicted values.
- Absolute eosinophil count and serum Ig E was assessed in all patients of each severity group.
- Among 100 patients, 55 were females and 45 were males.

- Most common age group in our study population was 26-32 years ,Range 18-48 years
- 56 among 100 had positive family history and there was positive correlation with family history and asthma severity.
- Most common risk factor in the study population was atopy and the most common associated comorbid condition was allergic rhinitis
- Other comorbidies in the study population were eczema, sinusitis, obesity and gastroesophagal reflex disease.
- Asthma comorbidity has a strong association with the severity of asthma in our study population(**(P Value <0.01)**
- Positive correlation between absolute eosinophil count and severity of asthma was statistically significant. **(P Value <0.01)**
- Serum immunoglobulin E levels also had positive correlation with severity of asthma which was statistically significant**.(P value<0.01)**

# CONCLUSION

**Based on our present study it was concluded that**

- Family history has a strong association with the disease and severity.
- Asthma was also associated with comorbidities like allergic rhinitis,obesity,gastroesophagal reflex disease.
- Comorbidity by the disease has adverse impact on people's health and health care system. Focusing to tackle such comorbidities is also crucial.
- Asthma comorbidity has a strong association with the severity of asthma
- Absolute eosinophil count has a definite positive correlation with asthma severity in the severe persistent asthma group.
- Mean serum Ig E in mild, moderate and severe persistent cases was 271.50 ,916.48,1662.59 IU/mL with positive correlation.
- Our present study advocates the possible supplementation of absolute eosinophil count and serum immunoglobulin E levels as another objective parameter that can help in selecting the appropriate severity level in asthmatics.
- Estimation of serum Ig E in diagnosed case of asthma gains importance with increasing severity based on clinical grading.

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# PROFORMA

Name :

Age:

Sex (M/F): Occupation:

Address:

Presenting complaints:

History of presenting complaints:

a) Cough:

- Frequency
- Severity
- Duration
- Aggravating Factors
- Relieving Factors

b) Wheezing

- Frequency- Daily/once a month /2-3 episodes yr/More frequent
- No of days attack usually last-1-2 days/week or more than 1 wk
- Relieving factors -subsides on its own or medications or nebulisation

C) Sneezing: Yes/ No

- Diurnal variation- early morning/ night
- Sleep- good/ occasionally disturbed/frequently disturbed
- Work/College absence-Days/ weeks

d) History of hospitalization: Yes / No

- Duration of stay
- Age of admission
- Management- antibiotics/ antihistamines/nebu]isation/don't know

e)History of pneumonia: Yes / No

X-ray proven - Yes /No

f) History of TB: - Yes/ No

- Any history of long standing cough/weight 1oss- yes/no
- Evening rise of temperature/night sweats

g) History of Allergy: Yes / No

- Dust/food/othersetc

Family history:

- H/o allergy in family:
- Bronchial asthma/urticarial/dermatitis/eczema
- Relation to patient:

Father/ mother/sibling/grand parent

- Any other diseases in family

Personal history:

a) Allergy to food items

Milk/banana/vegetables

b) Drugs

Aspirin/pencillin

**GENERAL EXAMINATION**

Built

Poor/moderate/well built

Nourishment

Poor, moderate/well nourishment

Pallor/cyanosis/clubbing/lymphadenopathy

Vital signs:

Pulse

BP

Anthropometry:

Weight

Height

SYSTEMIC EXAMINATION.:

**RESPIRATORY SYSTEM**:

Inspection:

- Shape of chest- symmetrical/asymmetrical
- Deformity –yes/ no
- Accessory muscles of action- yes/no

Pa1pation:

Trachea

Movement of chest wall- symmetrical/asymmetrical

Percussion

Hyper resonant/impaired/dull note

Auscultation

Rhonchi/ wheeze/ crepitation /others

**CVS:**

Heart sounds

**CNS**:

Cranial nerves

Motor system

Reflexes

Per abdomen:

**Investigations**:

CBC

Hb

TC

DC

ESR

AEC

Chest X ray

Serum Ig E

Lung Spirometry

Conclusion:

Severity of asthma:

Mild persistent

Moderate persistent

Severe persistent

Planned treatment:

Follow up:

# INFORMED CONSENT

## DEPARTMENT OF GENERAL MEDICINE

## COIMBATORE MEDICAL COLLEGE

Principal Investigator :

Research Guide:

Organisation:

Informed Consent:

Yourself , Mr/Mrs/Ms……are being asked to participate in the research study title "Correlation of serum immunoglobulin E levels and absolute eosinophil count with severity of bronchial asthma as assessed by lung spirometry '' Coimbatore Medical College hospital conducted by Dr.PriyaSeeraj,Post graduate in the Department of General Medicine,Coimbatore Medical College.You satisfy eligibility as per the inclusion criteria.You may ask any question before agreeing to participate.

**Research Being done:**

A STUDY ON CORRELATION OF SERUM IMMUNOGLOBULIN E LEVELS AND ABSOLUTE EOSINOPHIL COUNT WITH SEVERITY OF BRONCHIAL ASTHMA AS ASSESSED BY LUNG SPIROMETRY

**Procedures involved**

Detailed history with clinical examination

Routine haematological tests

Chest Xray

Serum Immunoglobulin E

Absolute eosinophil count

**Decline from participation**

You have the option to decline from participation in the study existing protocol for your condition

**Privacy and Confidentiality**

Privacy of individuals will be respectedand any information about you or provided by you will be strictly confidential.

**Authorization to publish results**

Results of the study may be for scientific purposes and or presented to scientific groups,however you will not be identified.

**Statement of Consent**

I volunteer and consent to participate in the study.I have read the consent or it has been read to me.The study has been fully explained to me and I may ask questions at any time.

…… ……..

Signature/Left thumb impression Date

(Volunteer)

……. ……

Signature of witness Date

## Key To Master chart

Sex

M-Male

F-Female

Sex Code

Male-1

Female-2

AH-Allergy history

DA-Dust allergy,FA-Food allergy,N-No specificallergy,O–Others

FH-Family history

Y-Yes

N-No

CM-Associated comorbid condition

AR-Allergic rhinitis

S- Sinusitis

E-Eczema

GE-Gastro esophagal reflex disease

O-Obesity

N-None

S-Symptoms

W-Wheeze,D-Dyspnea,NA-Nocturnal Awakenings,C-Cough

F/wk-Frequency of need for reliever treatment/week

FEV1%P -Forced expiratory volume in 1 st sec %Predicted

Pre bro-Prebronchhodilator

Post bro-Postbronchodilator

Rev%- Reversibility % postbronchodilator therapy

S.Ig E-Serum immunoglobulin E

AEC-Absolute eosinophil count

G-Grade according to GINA(Global initiative for asthma guidelines)

UC-Uncontrolled

PC-Partly controlled

C-Controlled

Severity

M-Mild persistent

Mo-Moderate persistent

S-Severe persistent

**ஒப்புதல் படிவம்**

பெயர் :

பாலினம் : வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவத் துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவர் மேற்கொள்ளும் **"ஸ்பைரோமெட்ரி கொண்டு அறியப்பட்ட ஆஸ்த்துமா நோயாளிகளில் ஏற்படும் அதிக பாதிப்பிற்கும், இரத்தத்தின் ஈஸ்னோ .்பில் அணுக்களின் எண்ணிக்கைக்கும், மற்றும் இம்முனோகுளோபுலின்** "ஈ" **அளவிற்கும் உள்ள தொடர்பு"** குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடனும், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :

# MASTER CHART

| Sl No | Name | Age | Sex | Sex code | AH | FH | S | F/Wk | FEV1 %P | | | Severity | G | AEC (/cu.mm) | S.IgE (IU/ml) | CM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Pre bro | Post Bro | Rev % | | | | | |
| 1 | Uma S | 38 | F | 2 | DA | Y | W,D,NA | >2 | 62 | 74 | 12 | Mo | UC | 380 | 1242 | N |
| 2 | Sharmila | 24 | F | 2 | DA | Y | W,NA | >2 | 25 | 37 | 12 | S | UC | 520 | 740.65 | AR |
| 3 | Praveen | 18 | M | 1 | DA | Y | W,D | >2 | 61 | 76 | 15 | Mo | UC | 360 | 688 | N |
| 4 | Pushpa | 27 | F | 2 | DA | Y | W,D,C,NA | >2 | 82 | 96 | 14 | M | PC | 180 | 100.42 | N |
| 5 | Bani | 43 | F | 2 | N | Y | W,D | >2 | 65 | 77 | 12 | Mo | UC | 390 | 1762 | AR |
| 6 | Suresh | 18 | M | 1 | DA | N | W,D,C,NA | >2 | 30 | 42 | 12 | S | UC | 580 | 2500 | AR |
| 7 | Mahila | 35 | F | 2 | DA | N | W,D | >2 | 63 | 77 | 14 | Mo | UC | 480 | 355.8 | S |
| 8 | Mallika | 38 | F | 2 | N | N | W,D | >2 | 83 | 95 | 12 | M | PC | 210 | 104 | AR |
| 9 | Raji | 29 | F | 2 | DA,O | N | W,D,NA | >2 | 64 | 78 | 14 | Mo | UC | 290 | 1150.8 | N |
| 10 | Mallika | 28 | F | 2 | DA | Y | W,D,C,NA | >2 | 30 | 42 | 12 | S | UC | 460 | 1800 | AR |
| 11 | Selvan | 32 | M | 1 | N | N | W,D,C,NA | >2 | 70 | 84 | 14 | Mo | UC | 350 | 1764 | O |
| 12 | Laila | 40 | F | 2 | DA,O | N | W,D | >2 | 67 | 80 | 13 | Mo | UC | 540 | 1897.6 | N |
| 13 | Saravanan | | M | 1 | DA | Y | W,D | >2 | 50 | 62 | 12 | S | UC | 620 | 2210 | GE |
| 14 | Raju | 30 | M | 1 | N | Y | W,D,C | >2 | 63 | 70 | 17 | S | UC | 490 | 1387 | N |
| 15 | Pradeep | 27 | M | 1 | DA | N | W,NA | >2 | 82 | 98 | 16 | M | PC | 210 | 82.68 | N |
| 16 | Murugan | 38 | M | 1 | N | N | W,D | >2 | 76 | 88 | 12 | Mo | UC | 260 | 1110 | AR |
| 17 | Usha | 29 | F | 2 | DA | N | W,D,C | >2 | 66 | 78 | 12 | Mo | UC | 340 | 1256 | N |
| 18 | Biju | 31 | M | 1 | O | Y | W,D | >2 | 72 | 85 | 13 | Mo | UC | 460 | 107 | N |
| 19 | Radha | 36 | F | 1 | DA | N | W,D,NA | >2 | 48 | 62 | 14 | S | UC | 410 | 2146 | AR |
| 20 | Alagasamy | | | 1 | DA,O | Y | W,D | >2 | 43 | 60 | 17 | S | UC | 570 | 2162 | N |
| 21 | Mini | 22 | F | 2 | DA | N | W,D | >2 | 84 | 96 | 12 | M | PC | 230 | 760 | AR |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 22 | Girija | 29 | F | 2 | DA | N | W,D | >2 | 80 | 94 | 14 | M | PC | 120 | 98.2 | O |
| 23 | Sam Alex | | | 1 | DA | N | W,D,C | >2 | 72 | 87 | 15 | Mo | UC | 330 | 360 | S |
| 24 | Velusamy | | M | 1 | DA,O | Y | W,D,C | >2 | 33 | 50 | 17 | S | UC | 480 | 2600 | AR,O |
| 25 | Nurjahan | 40 | F | 2 | O | Y | W,D,C | >2 | 67 | 82 | 15 | Mo | UC | 370 | 97 | N |
| 26 | Antony | 41 | M | 1 | N | N | W,D | >2 | 75 | 90 | 15 | Mo | UC | 440 | 1210 | AR |
| 27 | Tamarai | 27 | F | 2 | DA | Y | W,D | >2 | 87 | 91 | 14 | M | UC | 140 | 76 | AR |
| 28 | Migavel | 18 | M | 1 | O | Y | W,D,C | >2 | 47 | 52 | 15 | S | UC | 490 | 576 | O,E |
| 29 | Veeran | 25 | M | 1 | DA | N | W,D | >2 | 82 | 95 | 13 | M | PC | 200 | 770 | N |
| 30 | Krishnan | 34 | M | 1 | N | Y | W,D,C | >2 | 61 | 77 | 17 | Mo | UC | 330 | 983 | AR |
| 31 | Manikam | 30 | M | 1 | DA | N | W,D,C,NA | >2 | 75 | 88 | 13 | Mo | UC | 430 | 117 | N |
| 32 | Sakti | 23 | F | 2 | DA | N | W,D | >2 | 77 | 90 | 13 | Mo | UC | 310 | 880 | N |
| 33 | Valli | 31 | F | 2 | N | N | W,D | >2 | 81 | 95 | 14 | M | PC | 110 | 180 | AR |
| 34 | Eswari | 38 | F | 2 | O | Y | W,D,C | >2 | 35 | 50 | 15 | S | UC | 360 | 1450 | N |
| 35 | Ishwarya | 19 | F | 2 | O | N | W,D | >2 | 69 | 76 | 17 | Mo | UC | 270 | 934 | AR |
| 36 | Aisha | 23 | F | 2 | FA,O | Y | W,D | >2 | 44 | 58 | 14 | S | UC | 490 | 1850 | N |
| 37 | Nalini | 32 | F | 2 | O | Y | W,D,C | >2 | 82 | 96 | 14 | M | PC | 170 | 236 | AR |
| 38 | Kumar | 26 | M | 2 | DA | Y | W,D | >2 | 63 | 80 | 17 | Mo | UC | 370 | 861 | N |
| 39 | Leksmi | 30 | F | 2 | O | N | W,D | >2 | 68 | 82 | 14 | Mo | UC | 390 | 768 | AR |
| 40 | Subiah | 34 | F | 2 | O | Y | W,D | >2 | 83 | 97 | 14 | M | UC | 120 | 300 | N |
| 41 | Jijo | 44 | M | 1 | O | Y | W,D | >2 | 40 | 58 | 18 | S | UC | 420 | 2374 | AR,O |
| 42 | Aruchamy | 31 | M | 1 | N | Y | W,D | >2 | 55 | 70 | 15 | S | UC | 390 | 1357 | AR,GE |
| 43 | Kasturi | 33 | F | 2 | O | Y | W,D | >2 | 71 | 87 | 16 | Mo | PC | 270 | 868 | N |
| 44 | Veena | 26 | F | 2 | O | Y | W,D | >2 | 73 | 88 | 15 | M | PC | 130 | 78 | AR |
| 45 | Santhosh | 35 | M | 1 | DA,O | Y | W,D | >2 | 84 | 98 | 14 | M | PC | 110 | 117 | N |
| 46 | Balan | 48 | M | 1 | O | Y | W,D | >2 | 45 | 62 | 17 | S | UC | 470 | 1882 | AR |
| 47 | Vijaya | 30 | F | 2 | N | N | W,D | >2 | 66 | 80 | 14 | Mo | UC | 310 | 990 | N |
| 48 | Liji | 29 | F | 2 | O | Y | W,D,C,NA | >2 | 48 | 63 | 15 | S | UC | 460 | 968 | N |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | Chandran | 32 | M | 1 | O | N | W,D | >2 | 71 | 88 | 17 | Mo | UC | 330 | 1116 | AR |
| 50 | Buvanesh | 23 | M | 1 | N | N | W,D,C | >2 | 63 | 81 | 18 | Mo | PC | 410 | 887 | E |
| 51 | Akila | 36 | F | 2 | DA | Y | W,D,NA | >2 | 62 | 74 | 12 | Mo | UC | 350 | 1132 | N |
| 52 | Lavanya | 24 | F | 2 | DA | Y | W,NA | >2 | 25 | 37 | 12 | S | UC | 510 | 745.65 | AR |
| 53 | Vijay | 18 | M | 1 | DA | Y | W,D | >2 | 61 | 76 | 15 | Mo | UC | 360 | 688 | N |
| 54 | Moly | 27 | F | 2 | DA | Y | W,D,NA | >2 | 82 | 96 | 14 | M | PC | 190 | 100.32 | N |
| 55 | Revathy | 43 | F | 2 | N | Y | W,D | >2 | 65 | 77 | 12 | Mo | UC | 350 | 1602 | AR |
| 56 | Ajeesh | 18 | M | 1 | DA | N | W,D,NA | >2 | 30 | 42 | 12 | S | UC | 510 | 2300 | E |
| 57 | Rani | 35 | F | 2 | DA | N | W,D | >2 | 63 | 77 | 14 | Mo | UC | 410 | 720.8 | N |
| 58 | Megha | 38 | F | 2 | N | N | W,D | >2 | 83 | 95 | 12 | M | PC | 200 | 124 | N |
| 59 | Kalpana | 29 | F | 2 | DA,O | N | W,D,NA | >2 | 64 | 78 | 14 | Mo | UC | 230 | 1150.8 | AR |
| 60 | Meera | 28 | F | 2 | DA | Y | W,D,C,NA | >2 | 30 | 42 | 12 | S | UC | 460 | 1800 | N |
| 61 | Ajith | 32 | M | 1 | N | N | W,D,C,NA | >2 | 70 | 84 | 14 | Mo | UC | 350 | 1364 | N |
| 62 | Mariya | 40 | F | 2 | DA,O | N | W,D,C | >2 | 67 | 80 | 13 | Mo | UC | 540 | 1097.6 | AR |
| 63 | Amutha | 28 | F | 1 | DA,O | Y | W,D | >2 | 43 | 60 | 17 | S | UC | 540 | 2142 | S |
| 64 | Gopika | 22 | F | 2 | DA | N | W,D | >2 | 84 | 96 | 12 | M | PC | 210 | 720 | N |
| 65 | Leela | 39 | F | 2 | DA | N | W,D | >2 | 80 | 94 | 14 | M | PC | 110 | 440 | AR |
| 66 | Palanisamy | 34 | M | 1 | DA | N | W,C,D | >2 | 72 | 87 | 15 | Mo | UC | 320 | 430 | N |
| 67 | Raman | 40 | M | 1 | DA,O | Y | W,C,D | >2 | 33 | 50 | 17 | S | UC | 460 | 2400 | AR |
| 68 | Gayatri | 34 | F | 2 | O | Y | W,C,D | >2 | 67 | 82 | 15 | Mo | UC | 370 | 567 | AR |
| 69 | Ganesh | 41 | M | 1 | N | N | W,D | >2 | 75 | 90 | 15 | Mo | UC | 410 | 1200 | S |
| 70 | Seeta | 28 | F | 2 | DA | Y | W,D | >2 | 87 | 91 | 14 | M | UC | 240 | 416 | N |
| 71 | Vijeish | 18 | M | 1 | O | Y | W,C,D | >2 | 47 | 52 | 15 | S | UC | 440 | 2456 | AR |
| 72 | Mukil | 26 | M | 1 | DA | N | W,D | >2 | 82 | 95 | 13 | M | PC | 190 | 570 | N |
| 73 | Rajesh | 37 | M | 1 | N | Y | W,D,C | >2 | 61 | 77 | 17 | Mo | UC | 320 | 973 | AR |
| 74 | Solomon | 31 | M | 1 | DA | N | W,D,C,NA | >2 | 75 | 88 | 13 | Mo | UC | 420 | 176 | N |
| 75 | Umaiba | 19 | F | 2 | DA | Y | W,D,C | >2 | 50 | 62 | 12 | S | UC | 630 | 2110 | S |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 76 | Srinivas | 30 | M | 1 | N | Y | W,D,C | >2 | 63 | 70 | 17 | S | UC | 430 | 1287 | AR |
| 77 | Surya | 27 | M | 1 | DA | N | W,D,NA | >2 | 82 | 98 | 16 | M | PC | 220 | 134.68 | N |
| 78 | Senthil | 38 | M | 1 | N | N | W,D | >2 | 76 | 88 | 12 | Mo | UC | 246 | 1210 | N |
| 79 | Priyanka | 28 | F | 2 | DA | N | W,D,C | >2 | 66 | 78 | 12 | Mo | UC | 330 | 1156 | N |
| 80 | Deepak | 32 | M | 1 | O | Y | W,D | >2 | 72 | 85 | 13 | Mo | UC | 410 | 917 | AR |
| 81 | Padmini | 34 | F | 1 | DA | N | W,D,NA | >2 | 48 | 62 | 14 | S | UC | 310 | 1046 | AR |
| 82 | Victor | 29 | M | 1 | DA,O | Y | W,D | >2 | 43 | 60 | 17 | S | UC | 470 | 962 | AR |
| 83 | Valli | 22 | F | 2 | DA | N | W,D | >2 | 84 | 96 | 12 | M | PC | 230 | 98 | GE |
| 84 | Devaki | 39 | F | 2 | O | Y | W,D,C | >2 | 35 | 50 | 15 | S | UC | 360 | 1450 | N |
| 85 | Tamarai | 18 | F | 2 | O | N | W,D | >2 | 69 | 76 | 17 | Mo | UC | 270 | 934 | N |
| 86 | Thilagavathy | 33 | F | 2 | FA,O | Y | W,D | >2 | 44 | 58 | 14 | S | UC | 490 | 1850 | S |
| 87 | Lekha | 32 | F | 2 | O | Y | W,D,C | >2 | 82 | 96 | 14 | M | PC | 170 | 236 | AR |
| 88 | Vadivel | 27 | M | 2 | DA | Y | W,D | >2 | 63 | 80 | 17 | Mo | UC | 360 | 831 | N |
| 89 | Suganti | 30 | F | 2 | O | N | W,D | >2 | 68 | 82 | 14 | Mo | UC | 390 | 768 | E |
| 90 | Annapurni | 34 | F | 2 | O | Y | W,D | >2 | 83 | 97 | 14 | M | UC | 120 | 300 | N |
| 91 | Jebaraj | 44 | M | 1 | O | Y | W,D | >2 | 40 | 58 | 18 | S | UC | 410 | 2374 | N |
| 92 | Katirvel | 31 | M | 1 | N | Y | W,D | >2 | 55 | 70 | 15 | S | UC | 230 | 1057 | E |
| 93 | Gitanjali | 36 | F | 2 | O | Y | W,D | >2 | 71 | 87 | 16 | Mo | PC | 270 | 888 | N |
| 94 | Rangi | 28 | F | 2 | O | Y | W,D | >2 | 73 | 88 | 15 | M | PC | 130 | 358 | AR |
| 95 | Hameed | 35 | M | 1 | DA,O | Y | W,D | >2 | 84 | 98 | 14 | M | PC | 100 | 117 | N |
| 96 | Muthu | 41 | M | 1 | O | Y | W,D | >2 | 45 | 62 | 17 | S | UC | 460 | 602 | N |
| 97 | Chitra | 30 | F | 2 | N | N | W,D | >2 | 66 | 80 | 14 | Mo | UC | 300 | 210 | N |
| 98 | Maratakam | 27 | F | 2 | O | Y | W,D,C,NA | >2 | 48 | 63 | 15 | S | UC | 430 | 918 | E |
| 99 | Narayani | 31 | F | 2 | DA | Y | W,D,C,NA | >2 | 30 | 42 | 12 | S | UC | 440 | 1700 | S |
| 100 | Shiva | 30 | M | 1 | N | N | W,D,C,NA | >2 | 70 | 84 | 14 | Mo | UC | 310 | 904 | AR |