"TO STUDY THE CLINICAL PROFILE OF ASTHMA IN CHILDREN AND TO ESTIMATE THE SERUM MAGNESIUM LEVELS IN ASTHMATICS AND ITS CORRELATION WITH ASTHMA"

Submitted by

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In

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Under the guidance of

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LIST OF ABBREVIATIONS

Mg	**:**	**Magnesium**
mm	**:**	**Adenosine Deaminase**
AMP	**:**	**Adenosine monophosphate**
ATP	**:**	**Adenosine triphosphate**
ACH	**:**	**Acetyle choline**
CD	**:**	**Cluster of Differentiation**
CMI	**:**	**Cell Mediated Immunity**
IAP	**:**	**Indian Academy Of Pediatrics**
CAMP	**:**	**cyclic adenosine monophosphate**
IFN	**:**	**Interferon**
IL	**:**	**Inter Leukin**
IU/L	**:**	**International units per litre**
FEV_1	**:**	**Forced expiratory volume in 1 second**
mm	**:**	**Millimeter**
NK	**:**	**Natural killer**
PO_2	**:**	**Partial pressure of oxygen**
TLC	**:**	**Total lung capacity**
SD	**:**	**Standard Deviation**
yrs	**:**	**Years**

ABSTRACT

Objectives

This study was designed to measure serum ADA levels 6+/-1 week after BCG vaccination and to clinically compare them with matched controls to evaluate if this test can be used to measure cell mediated immunity evoked by BCG vaccination and to clinically compare tuberculin reactivity after BCG vaccination with ADA levels.

Methods

This study is carried out in the Department of Pediatrics, BLDEA'S Shri .B.M. Patil Medical College, Bijapur from November 1 2007 to July 2009. 30 Term healthy neonates were taken up from post natal wards of the hospital (study group), 30 Infants of 6 to 8 weeks of age who were not vaccinated earlier were taken as matched controls (control group). Serum ADA (Adenosine deaminase) estimation was done in the study group with in 24 hours of birth and 6 weeks after BCG vaccination and TST(Tuberculin skin test) was done clinically to compare tuberculin reactivity and ADA levels. Serum ADA levels were estimated in control group to compare them with the study group at 6 weeks.

CONCLUSION

The present study concludes that the rise in ADA levels 6 weeks after BCG vaccination is statistically significant; concluding cell mediated immunity is provided BCG vaccination. Also the ADA levels of the study group at 6 weeks compared to matched controls who were not vaccinated earlier is significant. Tuberculin skin test is the most common measure performed to evaluate the efficacy of BCG vaccination. The

present study showed a conversion rate of 96.67% and a positive correlation with the ADA levels. **The present study is the first of its kind to measure CMI after BCG vaccination in the form of increased ADA activity and to compare the same with TST.**

Key words: BCG vaccination, Serum ADA (Adenosine deaminase) levels, TST (Tuberculin skin test).

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INTRODUCTION

Definition of Asthma:

The word asthma has been used in the past to refer to almost any sort of difficulty in breathing, especially it was paroxysmal or episodic.

Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to a variety of stimuli and manifested by wide spread narrowing of the airways that changes in severity either spontaneously or as a result of therapy. The term “asthma” is not appropriate for the bronchial narrowing which results solely from widespread bronchial infection; eg: Acute or chronic bronchitis from destructive disease of the lung eg: pulmonary emphysema; or from cardiovascular disorders,. Asthma, as here defined, may occur in subjects with other bronchopulmonary or cardiovascular diseases. But in these instances, the airway obstruction is not causally related to these diseases [1].

The American Thoracic society has provided a definition [2]. “Asthma is a clinical syndrome characterized by increased responsiveness of the trachea bronchial tree to a variety of stimuli”. The basic definition then is expanded to include major symptoms (variable paroxysms of dyspnea, wheezing and cough), primary physiologic abnormalities (airway obstruction) and histologic changes (eosinophilic bronchitis).

Owing to chronic expiratory air flow limitation is a frequent symptom, especially in population with a high proportion of smokers and exposed to air pollution. It is variably associated with hypersecretion of bronchial mucous

(Bronchial catarrh). The terminology of resulting symptom complex is confused . It is variously called chronic obstructive lung or airway disease, chronic obstructive bronchitis or chronic bronchitis and emphysema[3]. Difference of opinion may arise about whether such patients should be said to be suffering from asthma.

Asthma is the leading chronic disease of childhood in industrialized countries. Despite advances in treatment, both mortality [5] and morbidity [6] rates from childhood asthma are increasing.

AIMS AND OBJECTIVES

To study the clinical profile of asthma in children attending pediatric outpatient department and admitted to pediatrics ward in **B.L.D.E.U's Shri. B. M. Patil Medical College Hospital and Research Center** and to estimate serum magnesium levels in asthmatics and its correlation with asthma.

REVIEW OF LITERATURE

In a study conducted by Paramesh.h[7.] The prevalence of asthma in Asian countries has increased. In a hospital based study in a journal of pediatric outpatient by pediatric pulmonologist on international guide lines" children under the age of 18 yrs in 2 decades from 1979- 1999 showed 29.5% suffering from asthma. The steady rise in prevalence correlated with demographic changes in the city, like increase in number of industries, increased density of population migration of rural population resulting in increased automobiles resulting in air pollution[7].

In another study conducted by, Reubin C Henry, Stanlay J et al, children with severe asthma were most likely to be males. Based on in vitro testing, children were significantly more sensitive of importance, children had less impaired lung function compared to the adults studied.[8]

Magnesium and lung function in a study conducted by Rhoades et al[9], it is generally thought that magnesium depletion leads to respiratory fatigue. Magnesium promotes healthy lung function by acting as a bronchodilator, preventing the bronchial passage going into spasm. Magnesium deficiency may increase vulnerability to allergies by increasing the release of histamine into the blood stream, increasing allergic reactivity in general.[9] Magnesium has been found to be deficient in many asthmatics during acute attacks, though actual levels may have been lower ,since blood level measurements do not detect soluble subtle tissue deficiencies. Low dietary intake of magnesium is associated with an increased incidence of asthmatic symptoms, wheezing and reduced lung functions. The administration of intravenous magnesium has been shown to be effective in the treatment of bronchial asthma symptoms.[10]

In another study, many factors in modern life tend to reduce many nutrients including dietary magnesium and its metabolic partner, potassium. This affects the population in the general and the asthmatics specifically. First, there are lower leads of minerals in food today due to depletion of the soil in modern farming methods. Modern methods of milling, processing and the preservation of food cause nutrient losses, eg 85% of magnesium is removed from whole wheat in the milling. Low dietary intake of magnesium is associated with an increased incidence of asthmatic symptoms, wheezing and reduced lung function. Other factors which drive down magnesium level in the population include stress, lack of sleep, exposure to noise, mainly through increased urinary excretion. Finally, many medications used in routine asthma treatment have specifically noted diuretic and or magnesium reducing side effects.[11]

In another study conducted by M.Sedighi et al[10], asthma is an important health care problem worldwide. It is the most common inflammatory chronic disease in childhood. Magnesium is the second most abundant intracellular cation. Many clinical studies linked, reduced magnesium concentration to many disease states, especially coronary heart disease, hypertension, pediatric pulmonary disorders and many others. Magnesium is involved in pathophysiological reactions related to asthma.

In another study conducted by Khosrow Agin. et al[11], a prospective case control study was performed on patient with chronic stable asthma in a hospital, 42 consequitive volunteer patients with chronic stable asthma according to definite criteria and healthy sex and age matched subjects were chosen. In the final result the significant difference between 2 groups were noted. Hypomagnesemia was detected in 40.5% of chronic asthmatic patients.

In another study conducted by Khalid S. et a[12], a total of 174 known asthmatics were taken and serum magnesium levels assayed and compared with 232 patients without asthma, there were only slightly lower level of magnesium in a study group of asthmatics.[12]

In another study conducted by William B. et al[13], magnesium deficiency elevates circulatory level of inflammatory cytokines and endothelines, thus causing asthma.

HISTORICAL ASPECT OF BRONCHIAL ASTHMA

Bronchial asthma was known from time immemorial onwards. But first description of asthma was about 2000 years afterwards.“Asthma” is a Greek word, means “panting”.

There are mentions regarding asthma in Hippocratic writings (460-370BC).But details were not known. In early Christian era Aretaeus who first described more clearly as asthma is due to dampness of the lungs by viscid humer. In (A.D 131-201) Galeus attributed that asthma is due to secretions coming down from the brain. In the seventh century Paulus Aegineth combining the Greek and Arabian concepts, he attributed the disease to “Thick and viscid humors becoming infarcted in the bronchial cell of the lung”

In India 500 death per year occur for every million. Till nineteenth century asthma could not be distinguished from bronchitis. Till 12th century the main aim of asthma treatment was to treat the accumulation of phlegm mentioned in his “Greatise on Asthma” by mainmonides, by giving chicken soup, fresh water fish, fennel, and parsley, organnum, mint and raddish.

Folk remedies

Ephedrine is used from time immemorial in Chinese remedies as treatment of asthma. Ancient physicians of India were using atropine for asthma, also used burned datura stromanenolum to release anticholinergic fumes. Egyptian people were using chromolyn from khella. In the 19th century tea and coffee were very popular as a source of theophylline for the treatment of asthma.[14]

Corticosteroids were also used in the past. Placenta and adrenal gland extracts were the sources of corticosteroids. Salt paper (Potassium Nitrate) were burned to produce bronchodialator fumes. Also mirajuana has got a bronchodilator effects.[15]

Emergence Of Anti-Asthmatic Drugs

Period		Drugs
3000 BC -200 AD	-	**Ephedrine (China, Greece)**
		Atropine (Middle East)
		Chromones (India)
200 AD -1000 AD	-	**Arsenic Smoke (Arab)**
1650 (Approximately)	-	**Ipecacuananha (Brazil)**
1786	-	**Strong Coffee**
1802	-	**Stramonium Cigarettes (England)**
1840	-	**Iodide, Potassium Nitrate Inhalation**
1900	-	**Adrenaline (Oral-by-US)**
1920	-	**Theophylline (Germany) Oral & IV**
1924	-	**Ephedrine**
1940	-	**Iso Proterenol (Germany)**
1948	-	**Corticosteroids (U.S.A)**
1950	-	**Isoetharine (U.S)**
1961	-	**Metaproterenol (Germany)**
1967	-	**Fenoterol (Gremany)**
1968	-	**Albuterol (England)**
		Chromozlin (England)
1969	-	**Terbutalin (Sweden)**
1972	-	**Bedeomethasine (England)**
1974	-	**Ipratropium (Germany)**
1990	-	**Salmeterol (England)**

Samuel Butler had commented about asthmatics as “Live under the shadow of death which is like a sword of democles that may fall at any moment”.

Dean Swift who was an asthmatic is said to have remarked that if he could once set the air of lungs out, would take care never to let it in again.

Although asthma is not caused by emotions or personality disorder but individual episodes can be incited by emotional upset. Certain foods, drugs, allergens like dust, pollens, or cold, exercise can aggravate changes of the lungs.

In the 14th century (1135-1204) a great physician to Saladin wrote a treatise on asthma called “Tractus coutra passionem asthmatics”.

In 16th century Milanese physician in 1552 was summoned to Scotland to treat Archbishop Hamilton of St. Andrew who was suffering from asthma due to specific irritants like feathers and leathers.

In the early 16th century Paracelsus who pioneered in chemistry related to origin of many diseases including asthma to metallic influences. His disciple Van Helmont stated that asthma is originated in the “Pipes of the lungs” and compared asthma to the failing evil (Epilepsy) of the mind. His great contribution was the association asthma with seasonal changes, inhalation of irritants, and ingestion of particular foods.

In 17th century Danniel Sennert believed that humors around the liver were carried by circulation to lungs and these cause obstruction to trachea and bronchi. A few decades later Thomas will has depicted the clinical features of asthma both clearly and successfully. According to him asthma is a terrible disease causing shaking of organs of respiration as in an earthquake , the direct cause being compression of the bronchi or obstruction by serous catarrh, purulent matter, or little

stones, vapours from the spleen, womb or bowel were also considered as contributory causes.

The first comprehensive book on asthma was published by John Floyer in 1948. According to him, the immediate cause of asthma is straightness, compression or constriction of the bronchi. Two types of asthma were described. The continued type and periodic type. In the continued type included tuberculosis, abdominal tumors and emphysema. In the periodic type come catarrh, hysteria and atmospheric changes.

In 1769 John Millar who first described asthma as a definitive clinical disease with its own mode of onset, clinical course and subsequent complications.

In modern Era Lennec had published "Classic Treatise on Auscultation" in 1819, he had defined asthma as a paroxysmal dypnoea occurring between two intervals of normal respiration with characteristic signs of sibilant and sonorous ronchi. He considers the etiology as chronic catarrh, cardiac enlargement. In his statement "I have met with many cases in which it was impossible after the most minute research to find any organic lesion whatsoever to which asthma could be attributed". He described two kinds of asthma without discoverable organic lesion.

(1) Asthma with puerile respiration occurring in case of chronic mucus catarrh.
(2) Spasmodic asthma which is a precursor of extrinsic and intrinsic asthma later.

In 1830 Eherle's published "Treatise on the Practice of Medicine". He had defined asthma as paroxysmal infection of the respiratory organs characterized by a great difficulty of breathing, tightness across the breast and a sense of impending suffocation, without fever or local inflammation. The concept of hay fever caused by emanation of pollen was introduced by Elliotson in 1831 and Salter in 1864. They

noticed that symptoms of asthma often occurred in case of hay fever. By the end of 19th century it was accepted that hay fever and asthma were related diseases and the concept of hypersensitivity was expanded by Muller in 1990. Meltzer in 1990 concluded that asthmatic seizures were the result of hypersensitivity in individuals previously sensitized to pollens, emanation from animals or products of digestion. The sensitization may be hereditary or acquired.

EPIDEMIOLOGY

Prevelence and Incidence

Asthma is a common disease affecting 9to12 million people in UnitedStates [4].

Asthma is a world wide disease. Nearly 5-10% of the population at some stage during life suffers from asthma. It can occur at any age. Usual occurrence is before 6 years of age (50%), another (30%) before 40 years of age. Males are more affected than females (2:1 ratio).

In India, 4-5% of the population is affected with bronchial asthma.

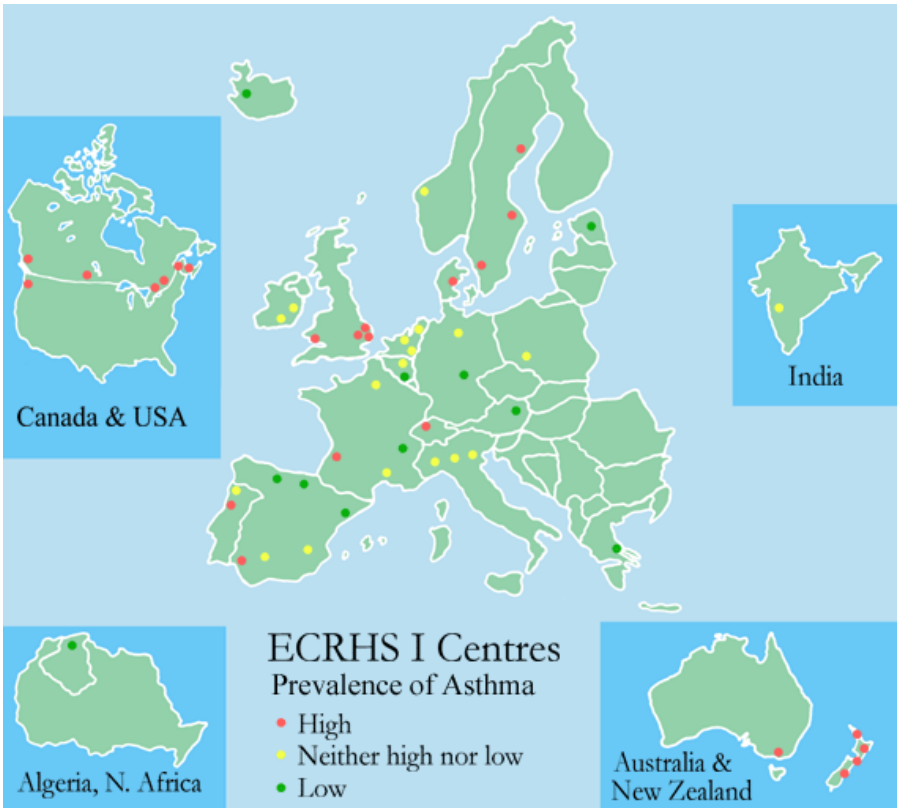


Figure 1. Prevalence of Asthma

(High- > 7 %, Neither high nor low- 4-5 %, Low - < 3 %)

DEFENITION OF BRONCHIAL ASTHMA

Bronchial asthma is a clinical entity and is said to exist when a patient is having paroxysms of reversible widespread airway obstruction leading to shortness of breath, wheeze and cough. The cause for obstruction being chiefly inflammation and smooth muscle contraction. This inflammation leads to hyper-responsiveness of airways to a variety of stimuli. The reversibility may be spontaneous or on treatment with drugs.

ANATOMY

DEVELOPMENT OF LUNG:

The Lung appears first as an epithelial bud as the caudal end of laryngotracheal group on the 26th day of ovulation. This bud derived from the endoderm will form the epithelium of the airways and of the acini. As it elongates, it becomes inverted in the mesenchyme derived from mesoderm, and the mesechyme layer exerts control over its pattern of branching. The mesechyme develops into the connective tissue, cartilage, smooth muscle and vessels of the lung. By about the 33rd day the trachea has become separated from the foregut and ponchis representing the five lobes are clearly apparent. Further division leads to the development of the full adult segments by the 41st day. And completions of bronchial tree, as far as the terminal bronchioles by 16th week.

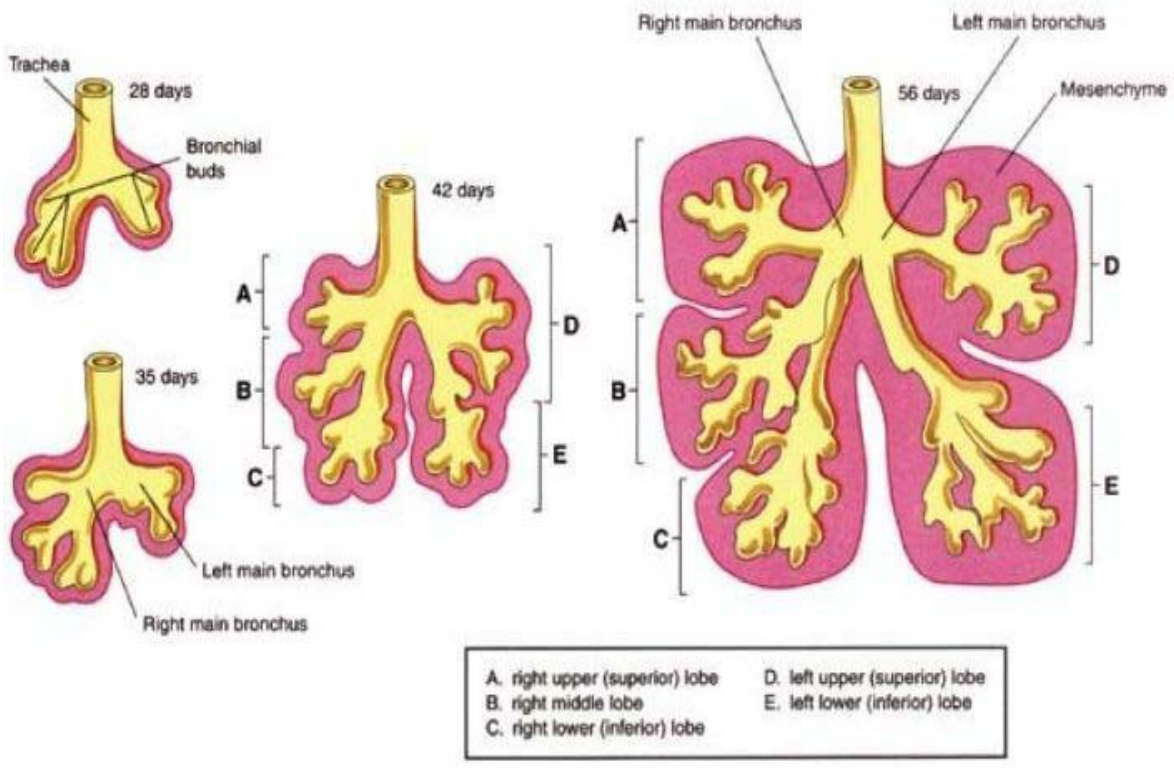


Figure 2, Development of lung

Trachea:

It extends from larynx till the bifurcation at the 5th thoracic vertebra. Its length averages about 10-12cm in the adult.

The trachea is related anteriorly to the remains of the thymus, the innominate vein, superior vena cava and azygos vein. Laterally aortic arch, the recurrent laryngeal nerve (runs up between the aortic arch and trachea). And the trachea divides in to right & left main bronchi. The ridge between bronchi is called carina.

Broncho – Pulmonary Segments:

The trachea divides into right & left main bronchi. The left runs more horizontally than the right, above the left atrium. It is about 5cms long and is related to aortic arch above, the descending aorta and thoracic duct posteriorly and pulmonary artery anteriorly. The right main bronchus, being a more direct continuation of the trachea, is the more usual path for inhaled foreign bodies to take. It is about 1-2.5cm long, and the pulmonary artery runs below and then anterior to it, while the azygous vein arches over it superiorly. The right main bronchus divides into right upper lobe bronchi, which in turn divides into apical, anterior and posterior. The intermediate bronchi supplies middle lobe and further divides into lateral and medial segments. The lower lobe bronchus divides into one apical and four basal like.. Anterior basal, Posterior basal, Lateral basal, and Medial basal.

The left main branch divides into upper and lower lobe bronchi. The upper bronchus divides into apico-posterior and anterior segments. And a lingular branch which in turn divides into superior and inferior bronchi.

The left lower lobe bronchus is further subdivided into four bronchi unlike that on the right side. Like Anterior basal, Posterior basal, Lateral basal and Apical (no medial basal).

The ultimate lung unit from each terminal bronchiole is called acinus. From the tracheal bifurcation till the smallest bronchi are reached after some 8-13 divisions. The smaller bronchi which are about 1mm diameter, divides further into 3-4 times before terminal one is reached . There are about 25000 terminal bronchi. Thus there are about 28 orders of divisions of the tracheo- bronchial tree. The total number of alveoli has been estimated to be 6 x 10^8.[16]

Blood supply:

The bronchial arteries from the aorta supply visceral and peritoneal pleura. And true bronchial arteries supply the bronchial tree. They also supply the nerves, walls of the pulmonary vessels, and intrapulmonary lymph nodes.[16]

Pulmonary artery:

It arises from the infundibulam of the right ventricle at the pulmonary valve, below aortic arch divides into right and left branches. The right branch divides into upper and lower branches at the hilum, which supply upper and middle, lower lobes respectively. Left main pulmonary artery runs laterally slightly upwards and divides into upper and lower branches, which subdivides as on the right side. It is related posteriorly to descending aorta to which it is connected by the ligamentum arteriosum (the remnant of the ductus arteriosus). And the left recurrent laryngeal nerve winds round the ligamentum arteriosum, which explains why left hilar disease may cause vocal cord paralysis.

Lymphatics of the lungs:

1. Upper 2/3 Right upper lobe: Right tracheo bronchial nodes.
2. Lower 1/3 Right upper lobe: Dorso lateral hilar nodes.
3. Right middle lobe: Hilar nodes around middle lobe branches.
4. Dorsolateral parts of left lower lobe: Dorso lateral hilar nodes.
5. Venteromedial parts of Right lower lobe: Venteromedial hilar and carinal nodes.
6. Apex left upper lobe: Para aortic nodes.
7. Rest of the upper lobe: Anterior and posterior hilar and carinal nodes.
8. Lower lobe: Similar to Right lower lobe.

Two lymphatic networks drain the lung. The superficial system arises in the pleura, the deep arises in connective tissues between the acini and around bronchi and vessels. Lymph drain finally into the systemic venous system at the junction of the subclavian and internal jugular veins in the thoracic duct on the left and the right lymphatic duct on the right.

ANATOMY OF THE AIRWAYS AND TERMINAL RESPIRATORY UNIT

The trachea divides into two main bronchi, the right and the left. The right main bronchus gives off an upper lobe bronchus, continues as intermediate bronchus and divides into middle and lower lobe bronchi. The left main bronchus divides into left upper lobe and left lower lobe bronchi. These lobar bronchi divide further into segmental, sub segmental and lobular bronchi. The walls of airways from Trachea to lobular bronchi are lined by pseudo stratified ciliated epithelium containing Goblet cells and their walls have mucous glands and cartilage. The bronchiole which follow lobular bronchi do not have mucous glands or cartilage in their walls. The terminal bronchiole which is the last of the purely conducting airways is lined by a single layer of ciliated epithelium. The Respiratory bronchioles which follow are partly lined by cuboidal epithelium.[10]

The Acinus

Loeshke in 1921 suggested that the Acinus be taken as the lung unit. The Acinus is that portion of the lung distal to the terminal Bronchiole. It is also called the terminal respiratory unit. It is fairly uniform in size measuring 7.5mm x 8.5mm. The terminal bronchiole is that bronchiole that immediately precedes a branch which contains alveoli in its wall. The first branch containing the alveoli is labeled as the respiratory bronchiole.

The pattern of branching distal to the terminal bronchiole usually follows a law of simple dichotomy. Occasionally the respiratory bronchioles may divide Acinus trichotomously or even quadriavially (pump, K K, 1964). There are usually 3 orders of Respiratory bronchioles in each acinus. As they proceed distally the Respiratory

Bronchioles carry progressively increasing numbers of alveoli, and are lined by cuboidal epithelium in between the alveolar openings. The respiratory Bronchioles give raise to about 5 orders (range3-9) of alveolar ducts. These alveolar ducts have no cuboidal epithelium and the openings of the alveoli are closely packed together in a helical, about 15 alveoli around each duct. Each last order alveolar duct opens into a alveolar Sac which has alveoli all round.

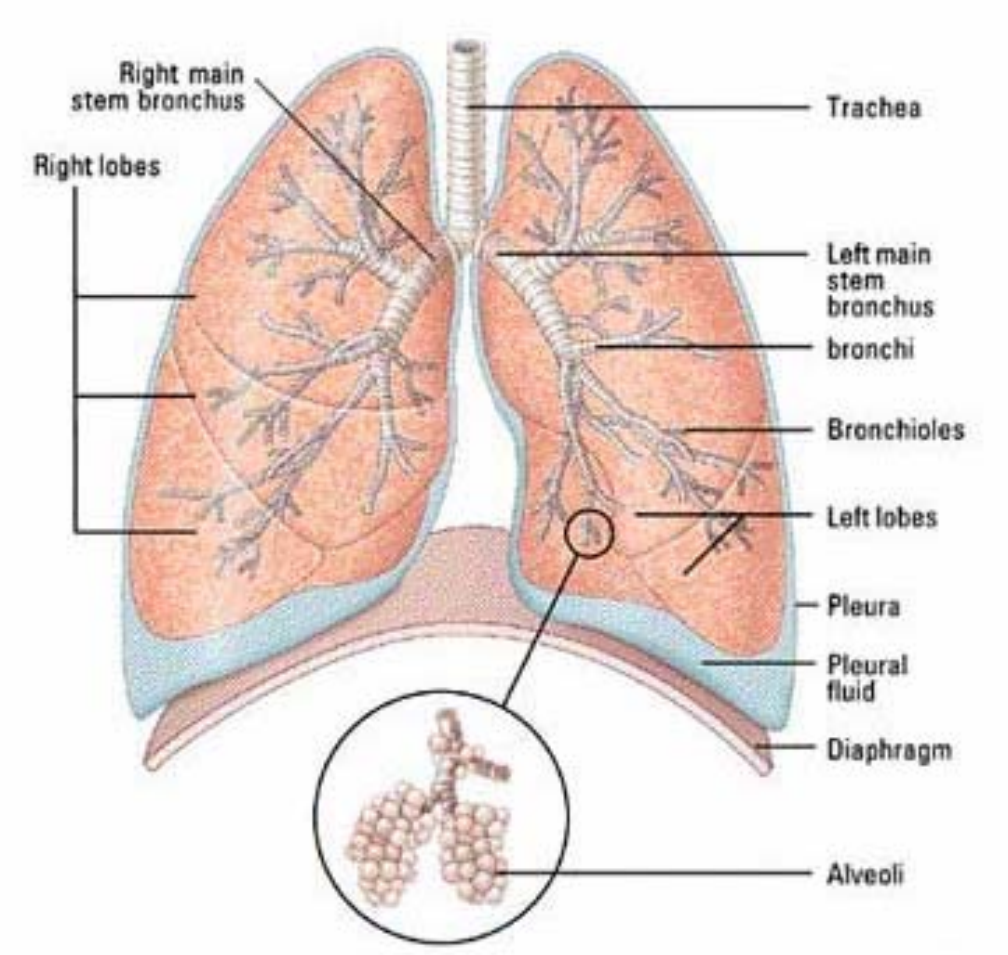


Figure 3. Lung & Alveoli

The alveoli are so closely packed together that they fill all available space. The arrangement can be likened to that of closely packed bubbles of soap.

The opening of the alveoli into the duct (Respiratory bronchiole or Alveolar duct or sac) is about 240 um in diameter. The maximum diameter of each alveolus is around 300 um.

The walls of the Alveoli are lined by a continuous layer of epithelial of two distinct types: Type I and Type II cells. The maximum diameter of each alveolus is around 300 um.

The walls of Alveoli are lined by a continuous layer of epithelial cells of two distinct types: Type I and Type II cells. The capillaries lie in the walls of the Alveoli. There are elastic and collagen fibers in the wall. A dense membrane of elastic and collagen fibers separates the Alveolar Components and interstitial space containing vessels and lymphatic's. The internal surface of the Alveoli is lined by the surface active agent the surfactant.

The type I alveolar epithelial cell is a flat cell with large surface area covering the major portion of alveolar surface. It has a central nucleus surrounded by rather thick cytoplasm which stretches out into thin wing like processes. The thin portion measures about 1mm in cross section and is intimately related to capillary endothelium with little interstitial tissue interposed in between. This part is said to constitute the gas exchange site.

The type II epithelial cell is cuboidal in shape, 10-15 mm thick and contains lamellar inclusion bodies. These cells occupy the corners of the alveoli and are said to be the source of surfactant.

There is another cell lying free in the alveoli. This is the pulmonary alveolar macrophage which is the most important defence mechanism in the alveoli. It measures about 12 mm and is actively phagocytic engulfing both bacteria and particulate material. It contains many enzymes in its lysosomes: Proteases,

Deoxyribonucleases, Ribonuclease, Beta Glucuronidase and probably elastase which help in killing the phagocytosed bacteria. Substances like Silicon Dioxide, Asbestos, Ozone, Cadmium and Cigarette smoke are toxic to the macrophages. These substances causes death of the macrophage with release of lysosomal enzymes. The enzymes thus liberated cause tissues damage by elastolysis which is being implicated in pathogenesis of Emphysema.

The number of alveoli in human lungs depends on the height and weight of the individual. There are 200-600 million alveoli, 13.6x10 alveolar ducts and sacs, and 3x10 -6x10 terminal Bronchioles in the lungs. Each acins has 12500 alveoli. The internal surface area of human lung is computed to be 50-82 square meters.[17]

Alveolar Pores : (Pores Of Kohn)

These are openings or discontinuation in the alveolar walls, about 5-15 um diameter. They are situated in the intercapillary part of the alveolar wall and are lined by alveolar epithelium. They are absent during prenatal and neonatal life. Their number increases with age. In adults each alveolus has 1-6 such pores.

Bronchiole-Alveolar Communications: (Canals of Lambert)

These are epithelium lined communication between distal bronchioles and some of the neighbouring alveoli. They are about 30 um in diameter.

Direct Airway Communications

These are collateral channels bigger than canals of lambert, observed in canine lungs. Their exact location and significance in the humans are not clear.

These Peripheral airway communications are the routes of collateral air draft between alveoli of the same acinus, in between different acini, lobules and even segments. Inter lobar air draft has also been demonstrated in normal human lungs.[18]

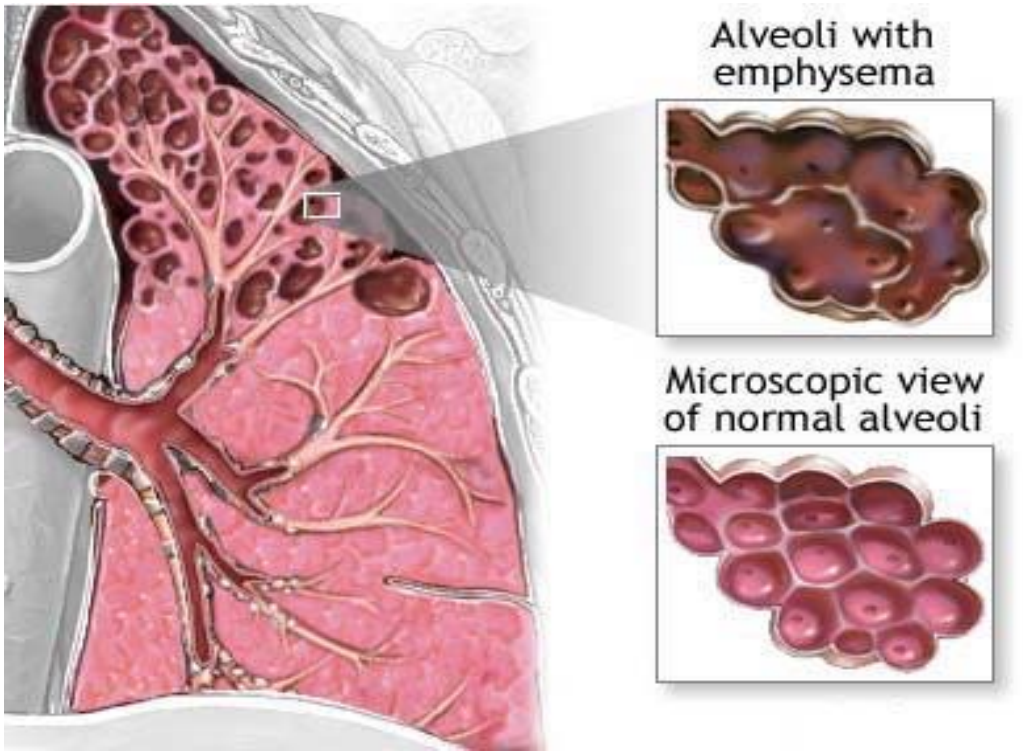


Figure 4. Alveoli in Normal and Emphysematous Lung

The branching pattern, diameters and volumes of airways :

The law of simple dichotomous branching cannot be applied to Bronchi. The conventional system of counting designates treachea as 0 orders, the main Bronchi as 1st order and so on, till the alveolar sacs are reached. The number of generations, by counting thus, depends upon the anatomical location of the segment. some segments have 15 generation and some have 25 generations. Thus there is asymmetry in bronchial tree division. In the conventional system a 10th order branch may be a terminal bronchiole in one segment or a lobular bronchus in another segment.

To bring uniformity to the nomenclature of the bronchial division, the Strahler system[18] of ordering has been suggested. In this system the counting is done from peripheral to the central branches. Airway with a diameter of 0.7 mm is counted as 1st order division. When two 1st order branches join, it becomes a 2nd order branch. When two 2nd order branches join the confluence it becomes a 3rd order branch and so on. But if a 1st order branch join a 2nd order the confluence continues to be a 2nd order branch. Thus when branches of like numbers join the confluence takes the next higher number. But when branches of 2 unlike numbers join the confluence retains higher of the two numbers.[18]

By employing this system there are 17 orders of airways in the lungs, the 17th being trachea and the 1st being the terminal bronchiole. The branching ratio is 2.74 i.e., each airways gives raise to 2.74 daughter branches. A linear relationship is found to exist between the log of the number of Branches and the order.

The pulmonary artery also has 17 orders of Branches, but its Branching ratio is 3, 4. Thus there are most first order branches of pulmonary artery. The terminal Bronchiole which is a first order branch divides further into respiratory bronchioles,

alveolar ducts and finally alveoli. Each alveolus receives a first order twig of pulmonary artery.

The diameters of airways also show a close relationship with the order. The diameter of each airway diminishes from proximal to distal branch till the order No.6 is reached where it levels off and does not diminish beyond that, retaining a diameter of 0.7mm.

The total volume of airways from 1st order to the mouth is 150ml from 1st order to carina it is 70ml. The volume of the respiratory exchange unit beyond the terminal bronchioles is 3,200ml.[17]

PATHOPHYSIOLOGY OF BRONCHIAL ASTHMA

The pathophysiologic hallmark of asthma is reduction in airways diameter, brought about by edema of the bronchial wall, constriction of smooth muscle, vascular congestion, and tenacious secretions.

Airways obstruction is the primary pathophysiologic consequence of the process in the airways. Lung function is monitored by spirometry, the average forced expiratory volume in 1 second (FEV1) in adult population was approximately 1 liter or 30 to 35% normal.[19]

The net results is an increase in airway resistance, decreased forced expiratory volumes and flow rates, hyperinflation of lungs and thorax, increased work of breathing, alterations in respiratory muscle function, changes in elastic recoil.

Vital capacity tends to be <50% of normal, hypoxia is usual during acute exacerbations and have hypocapina and respiratory alkalosis. In severe bronchospasm metabolic acidosis can also be seen. Cyanosis is a very late sign.

The sign of CO_2 retention such as sweating, tachycardia, wide pulse pressure are seen. Also signs of acidosis such as tachypnoea, (do not have great value in predicting H_2 excess) can be seen.

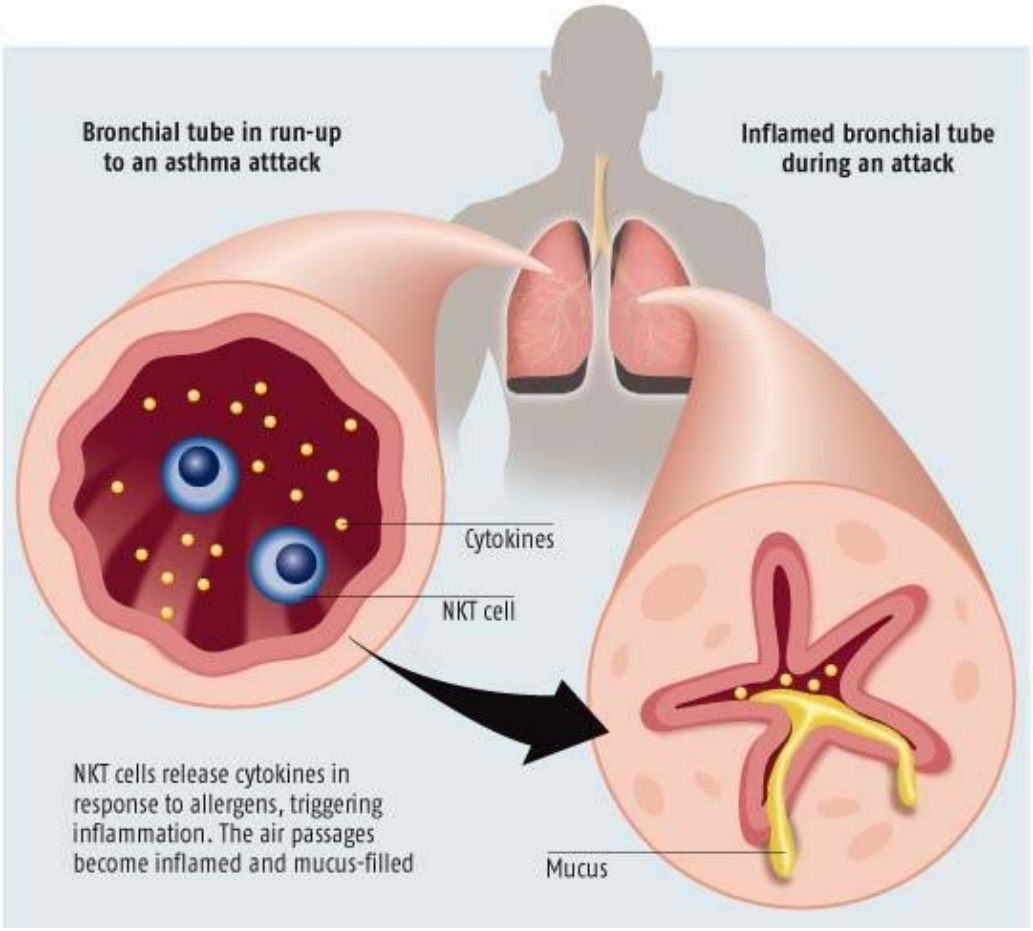
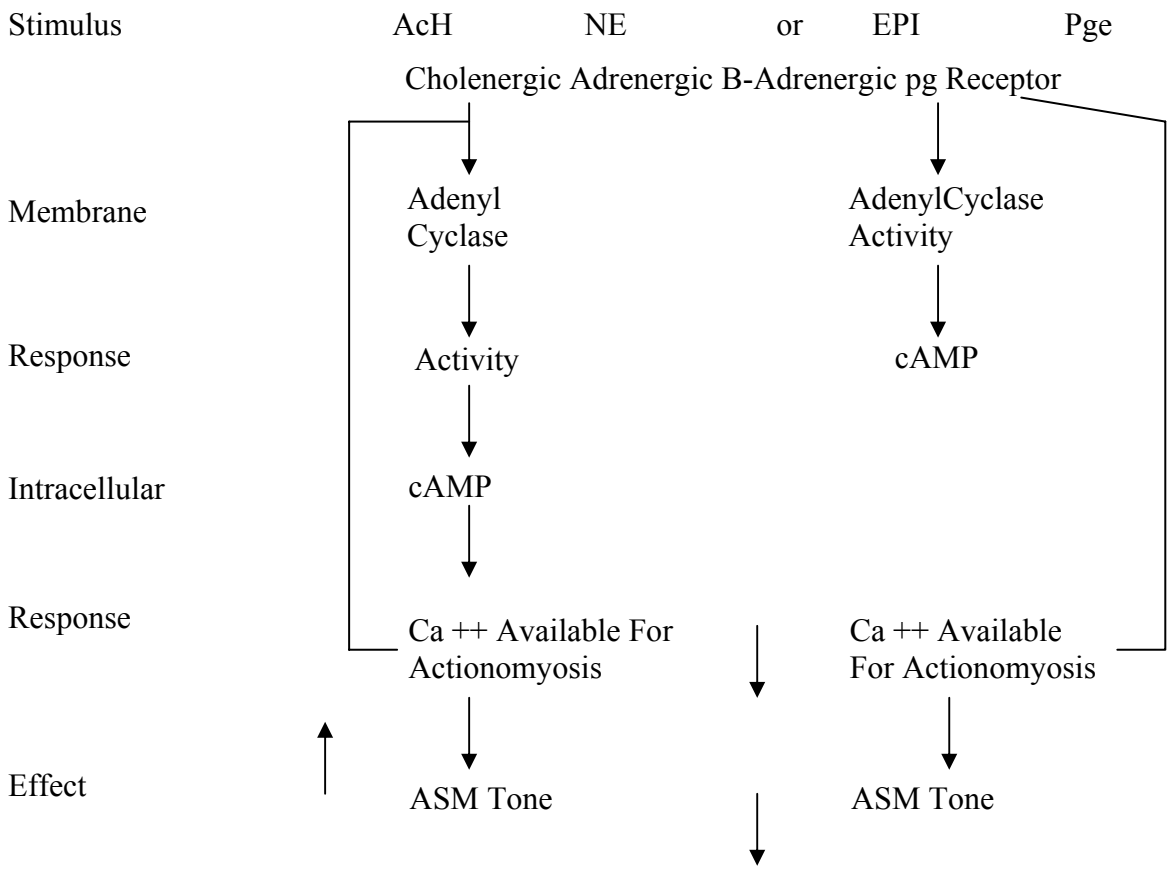


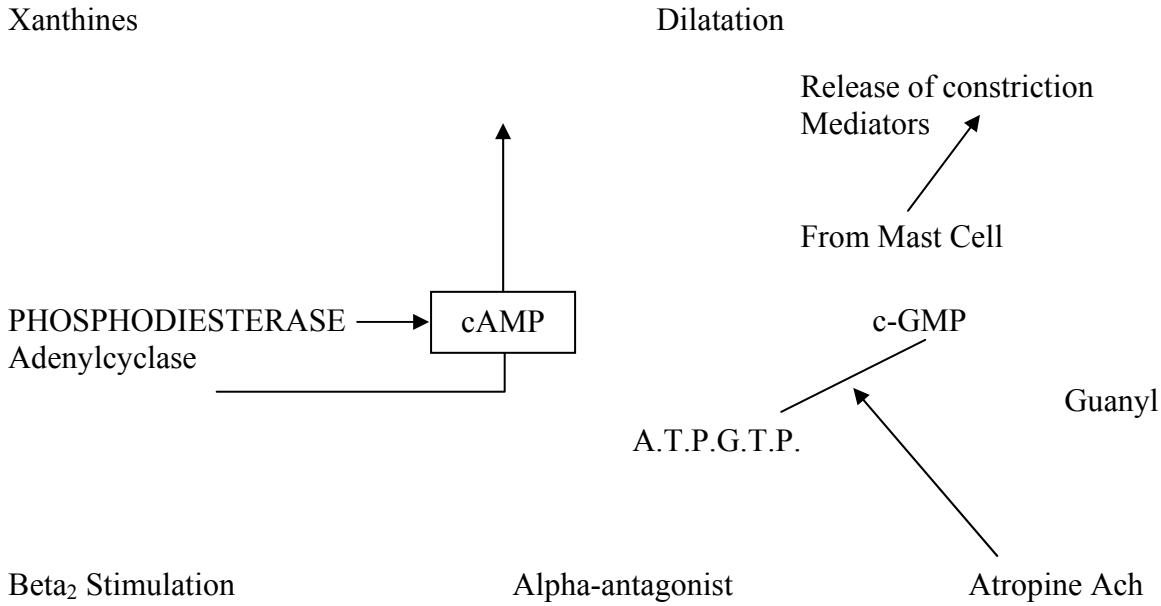
Figure 5. Bronchial tube in Asthma

PHYSIOLOGY

REGULATION OF AIRWAY SMOOTH MUSCLE TONE.



FACTORS AFFECTING LEVELS OF CYCLIC AMP AND CYCLIC GMP



Applied Physiology Of Respiration :

Respiration is the process concerned with gas exchange between an organism and its environment. In higher animals this process is usually subdivided into functional divisions.

Ventilation

Diffusion

Perfusion

Blood gas transport.

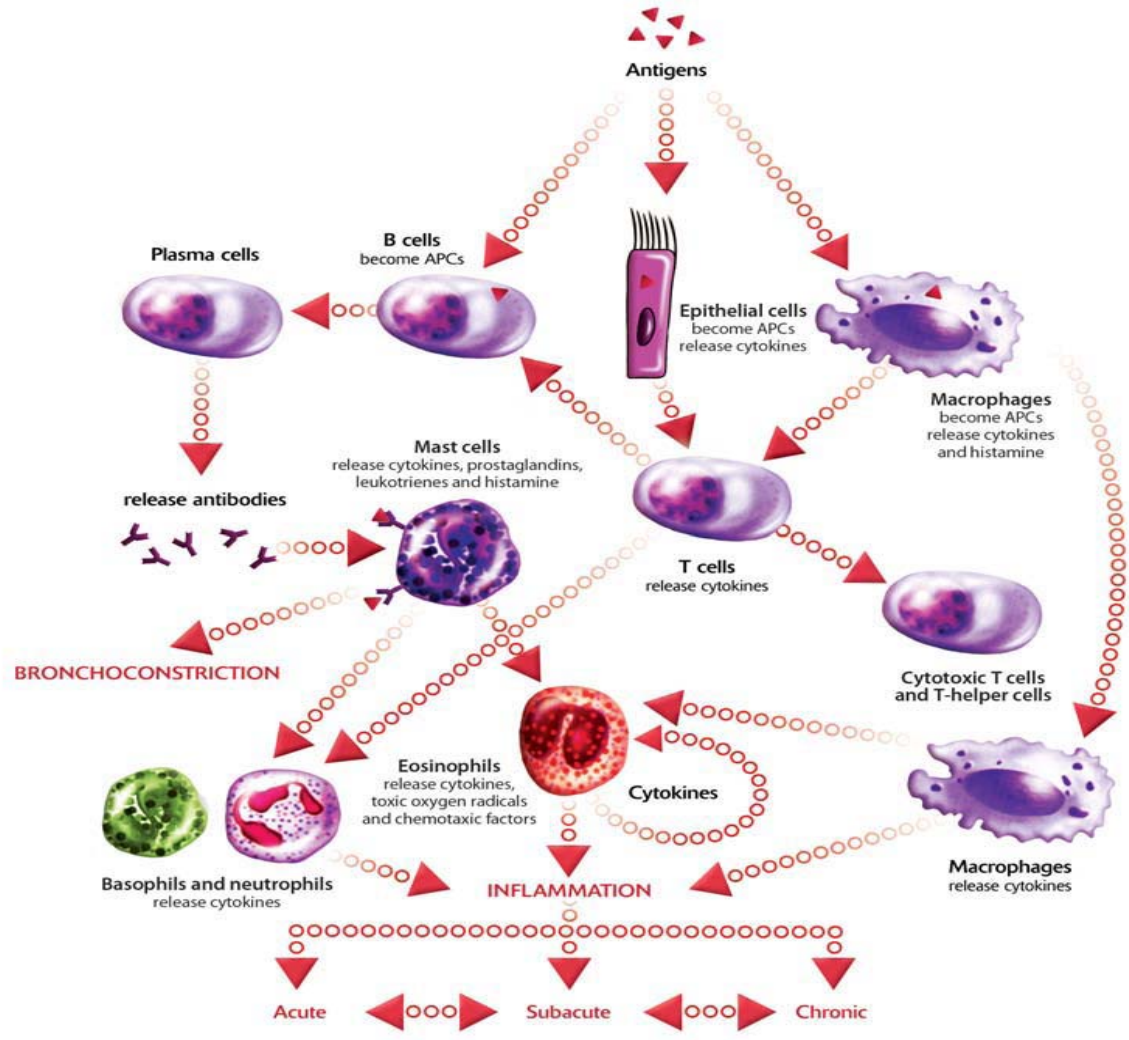


Figure 6. Pathophysiology of Bronchial Asthma

Ventilation

This is the movement of air between the outside and inside of lungs and its distribution within the tracheobronchial system and the gas exchange units.

Ventilation can be controlled voluntarily or it can occur automatically through feedback mechanisms involving the afferent stretch receptors in the alveoli, sensors of PH and PCO_2 in carotid body, aortic body and medulla, a central ventilatary control integrator in medulla and efferent innervating the inspiratory muscles actively expand the volume of the chest below producing an increase in the negative intrathoracic pressure causing air to enter lungs. This inspired air is distributed throughout the lungs but its distribution is not uniform because of the vertical gradient in pleural pressure that exists from top to bottom in the erect lung. This results in more of inspired air distributed to the lung base.

Expiration of gas to air spaces beyond collapsed or closed airways in chronic airflow obstruction may be possible through collateral channels such as the pores of kohn[19.]

This mechanism presumably accounts for the rarity of atelectasis in chronic airflow obstruction.

Expiration occurs passively due to elastic recoil of lungs. The rate of flow in airways and distribution of inspired gas is governed by the forces of respiration, the caliber of the airways and the elasticity of lungs.

Access of gas to air spaces beyond collapsed or closed airways in chronic airflow obstruction may be possible through collateral channels Such as to the pores of kohn[19].This mechanism presumably accounts for the rarity of atelectasis in chronic air flow obstruction.

Lung Volumes and Capacities

The lung volumes are divided into (Fig.7).

(i) Residual Volume (RV)

(ii) Expiratory Reserve Volume (ERV)

(iii) Tidal Volume (VT or TV)

(iv) Inspiratory Reserve Volume (IRV).

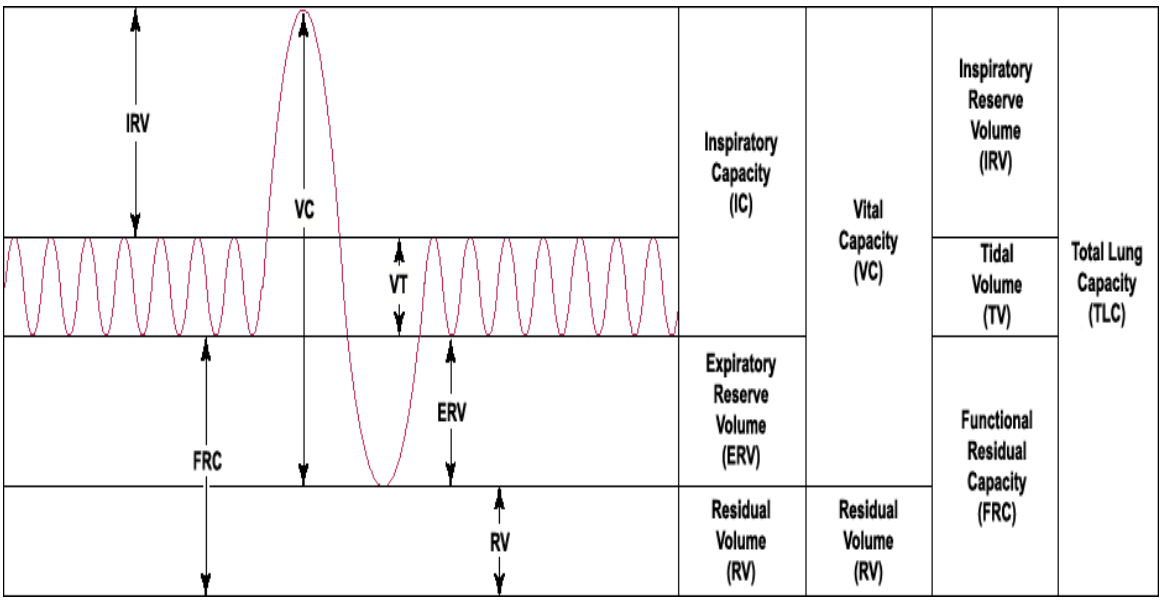


Figure 7. Lung Volumes

Residual Volume (RV).

This is the volume of the gas remaining in the lungs after a maximal expiration. This volume is about 20-25% of the total lung capacity. This is increased in diseases causing airway obstruction and decreased in diseases causing reduction in the amount of functioning lung tissue or limitation of chest wall or diaphragmatic movement.

Expiratory Reserve Volume (ERV)

This is the maximum volume of gas that can be expired from the end expiratory level. At rest it is about 15% of total lung capacity.

Inspiratory Reserve Volume (IRV)

This is the maximal volume of gas that can be inspired from end inspiratory position. At rest it is about 50% of total lung capacity.

Tidal Volume (VT or TV)

This is that maximal volume of gas that can be expired after a maximal inspiration. In healthy-adults it is 70-80% of TLC. It is a very useful screening test. It is reduced in diseases producing (i) reduction in the amount of functioning lung tissue.(ii) limitation of lung or thoracic wall or diaphragmatic move. (iii) obstruction to airways.

Inspiratory Capacity (IC)

This is a maximal volume of gas which can be inspired from the resting expiratory level.

Functional Residual Capacity (FRC)

This is the volume of gas remaining in the lung at resting expiratory level. Normally it is about 40 % of TLC. An increase in FRC indicates that lung is hyperinflated during quiet breathing. Thus it is common feature of chronic obstructive lung diseases. FRC is reduced in diseases causing reduction in functioning lung tissue, limitation of chest wall or diaphragmatic movement.

Residual Volume-Total Lung Capacity Ratio (RV/TLC)

Normally it is less than 30%. It represents the proportion of TLC that cannot be used to increase ventilation. In general, the ratio is increased in diseases causing chronic airway obstruction and is normal or reduced in restrictive disorders.

Alveolar and Dead Space Ventilation

Of the inspired Tidal air of about 500ml, 150 ml fills the airways and does not participate in gas exchange. This is the "Anatomic Dead Space". Physiological dead space includes anatomical dead space and the amount of gas ventilating alveoli without perfusion. This physiological dead space is more appropriately called the wasted ventilation (V_w or V_D) and can be calculated from the modified Bohr equation:

$$VD = \frac{PACO_2\text{-}PECO2}{PACO_2} \times V_E$$

P_ACO_2 : Partial pressure of CO_2 in arterial blood.

P_ECO_2: Partial pressure of CO_2 in expired air.

V_E : Volume expired.

The wasted ventilation is important in that, if it is increased the tidal volume should also be increased proportionately to maintain alveolar ventilation.

Alveolar ventilation is the air ventilating functioning alveoli. It is about 350 ml. This air mixes with the functional residual capacity gas in alveoli by diffusion. It is measured indirectly using the formula:

$V_A = V_T - V_D$

V_A = Alveolar Ventilation

V_T = Tidal Volume

V_D = Wasted Ventilation

Since CO_2 retention is a feature of alveolar hypoventilation, a raise in arterial CO_2 pressure above 14mm Hg also indicates alveolar hypoventilation.[20]

Alveolar hyperventilation in its pure form is uncommon, being seen in conditions producing depression of respiratory centre due to disease or drugs. In clinical practice alveolar hypoventilation occurs with any abnormality which reduces vital capacity. In these instances it is associated with other functional derangements.

Compliance

Both lungs and chest wall are distensible structures with elastic properties and different resting volumes. Thus at F.R.C. the lungs tend to collapse and the chest wall tends to expand resulting in a negative intrapleural pressure.

The elastic forces of the lung are due to its elastin and collagen containing structures and the surface tension of surfactant. Hence when they are distended a recoil pressure is generated. This recoil pressure governs the lung volumes, the distensibility and indirectly the flow rates by its effects on airways.

The distensibility or compliance of the lung is used to express the elastic property of lung in a simple way. Compliance is defined as the change in volume (ΔV) produced by a given change in pressure. (ΔP).

Compliance of lung (CL) = $\frac{\Delta V}{\Delta P}$

The compliance depends upon the volume of lung at which it is measured. It is higher at RV and lower at TLC, that is, lung is more distensible at lower lung volumes. The normal compliance is about 0.2L/Cm of Water.

The compliance is measured in static or in dynamic conditions. In static measurements the pressure and volume are measured at interrupted intervals and compliance calculated. In Dynamic compliance measurements are made when the subject is breathing continuously at different frequencies. Normally up to a respiratory frequency of 100 both dynamic and static compliance are equal. Fall in dynamic compliance indicates decreased elastic recoil or airway obstruction. Pulmonary compliance is reduced in pulmonary fibrosis etc. static compliance is increased in Emphysema but dynamic compliance is reduced and shows marked frequency dependence[20.]

The chest wall also exhibits elastic properties. Its compliance is reduced in a number of conditions affecting chest wall like scoliosis, pectus excavatum, thoracoplasty and in marked obesity.

Dynamic Properties

To cause air to flow into the lungs the inspiratory effort should overcome both elastic and non elastic resistance. The elastic resistance is governed by the compliance of lungs and chest wall. The non elastic resistance includes the frictional resistance of tissues to movement and the resistance to airflow in the airways due to friction and turbulence. Normally the inertia of tissues is too small.

Resistance to flow in a tube depends upon the pressure difference (p) between the ends of the tube and volume of flow through the tube (Q) and is expressed as:

n = Velocity of flow

$$\text{Resistance (R)} = \frac{\Delta P}{Q} = \frac{8\ nl}{\Pi R4}$$

L = Length of tube

R = Radius of tube

Measurements of pressures can be done using plethysmograph. But simple tests like measuring flow rates (FEV1) are enough for routine use[20]

As seen from the equation small changes in diameter of the tube can produce profound changes in resistance.

Normally in the lung, the diameter of airways diminishes as they proceed distally, but their cross sectional area increases. Hence the airway resistance decreases progressively from mouth to peripheral airways. The bulk of airway resistance is situated in airways of orders18-12. These airways are all subsegmental in location. The resistance to flow in small airways (<2mm) is only 10-30% of total airway resistance. Extensive changes can occur in these small airways without greatly affecting the airway resistance and hence this zone of small airways is called the silent zone.

More sensitive tests like spirometry are needed to detect the early changes in small airways.

Airway resistance can increase not only in diseases of airways but also in parenchymal disease. The elastic tissues of lung exert a radial force on the airways and keep them patent. A loss in elastic recoil can cause premature collapse of small airways during expiration and can thus increase resistance to airflow. The airway resistance can be indirectly estimated by measuring the volume of air expired forcibly in 1 second (FEV_I), its ratio to VC, by measuring peak expiratory flow rate (PEFR),

maximal expiratory flow rate (MMFR or FEF 200 – 1200)Maximum Mid-expiratory flow rate (MMFR or FEF 25-75%) and by flow volume curves.

Abnormalities of Ventilation

The lung disorders causing abnormalities of ventilation are usually divided into two categories: Restrictive and obstructive. This division is not completely satisfactory since it ignores the distribution of ventilation.

The restrictive disorders are due to restriction or limitation to the amount of gas that can be contained in the lung. They are seen in lung resection, chest wall deformities, parenchymal infiltration, pleural disorders and space occupying lesions in thorax.

The obstructive disorders are due to increased resistance to airflow as in asthma, Bronchitis, Emphysema, Bronchiectasis etc.

TEST	RESTRICTIVE	OBSTRUCTIVE
Vital capacity	Decreased	Decreased or Normal
Residual volume	Decreased	Increased
Total lung capacity	Decreased	Increased or Normal
RV/TLC ratio	Normal	Increased
FEV_I / FVC	Normal & increased	Decreased
MEFR (FEF200-1200)	Normal & increased	Decreased
MMFR (FEF25-75%)	Normal & increased	Decreased

Diffusion

This is the movement of 0_2 and CO_2 across the alveolar – capillary membrane, between the gas in the alveolar space and blood in the capillaries. This gas molecules move by virtue of their kinetic energy from an area of higher concentration to an area of lower concentration (partial pressure). The rate of Diffusion depends upon many factors including area available for diffusion, time available, the pressure gradient, the thickness of the alveolar capillary membrane and the diffusion co-efficient for the membrane.

The diffusion capacity (D_L) for any gas (G) indicates the quantity of that gas that diffuses across the alveolar capillary membrane per unit time (V_G) in response to the difference in main pressures of the gas within the alveolar (P_{AG}) and pulmonary capillaries (P_{cg}).

$$DLG = \frac{V_G}{P_{AG} - P_{CG}} \text{ ml/min/mm.}$$

The differing capacity tests for carbon monoxide are not as greatly affected by the abnormal V/Q as are the arterial blood gases. While steady – state measurements of carbon monoxide diffusing capacity are sometimes reduced in bronchospasm is present, the single breath measurement is usually normal even in presence of significant airflow obstruction. Increase in steady state measurements. Increase in single breath measurements in acute asthma suggest that regional shifts in perfusion to the lung apices enhance diffusion perfusion ratios, and possibly explain a higher single breath measurement.[21]

The diffusion can be interfered by abnormalities in any of the factors mentioned. Thus an increase is thickness of the alveolar capillary membrane, as in diffuse interstitial pulmonary fibrosis, sarcoidosis, asbestosis farmers lung etc. can reduce the diffusion. This is called the alveolar capillary block syndrome. But recent work has suggested that the alveolar capillary block syndrome is not important in these conditions in causing hypoxia and that ventilation perfusion anomaly is more important.

The diffusion capacity is increased in Asthma during an attack. The mechanism is not clear and is probably due to recruitment of capillary bed.

In routine clinical practice measurements of diffusion-capacity is done using carbon monoxide.

Perfusion

The pulmonary circulation delivers blood in a thin film to the gas exchange units. The whole of the output of the right ventricles, about 5L/min at rest, is accommodated in the pulmonary vascular bed at a low pressure. The pulmonary vascular tree acts as a high flow/low pressure system at rest and is greatly distensible being able to accommodate 3 times the normal flow with only a slight raise in pressure.

The pulmonary artery pressure at rest is 20/10mm Hg with a mean pressure of 14mm Hg. The pulmonary vascular resistance offered to flow of blood in pulmonary vascular tree and is expressed as:

$$\text{Pulmonary vascular resistance} = \frac{P_{PA} - P_{LA}}{Q}$$

P_{PA} : Pressure in pulmonary artery

P_{LA} : Pressure in left atrium

Q : Volume flow in unit time

This is normally = 0.95mm Hg/L/Min.

The pulmonary blood flow is not uniform in all the zones of the lungs due to effect of gravity in the erect lung. The perfusion is minimal at apices and gradually increases towards base.[22]

In an upright subject the lungs can be divided into three perfusion zones by the relative magnitude of pulmonary arterial, venous and alveolar pressures.

In zone I which is in or near the apex arterial pressure is less than alveolar and there is no flow since the vessels are exposed to alveolar pressure and collapse.

In zone II arterial pressure exceeds alveolar pressure which in turn exceeds venous pressure. Here the unit acts as a starling resistor and the flow is determined by difference between arterial and alveolar pressure. The blood flow increases down the zone since the arterial pressure increases down the zone and alveolar pressure remains constant.

In zone III venous pressure exceeds alveolar which in turn is exceeded by arterial. Here the flow is dependent on arteriovenous pressures and further increases down the zone.

In healthy subject in erect posture most of the lungs is in zone III. There is usually a small zone II near the apex and negligible zone I[22].

Perfusion of The Terminal Ventilatory Unit

The flow to a single acinus is 2.7×10^{-3} m1/ses and to a single alveolus is 2.7×10^{-7} m1/sec. The linear velocity of flow in branches supplying alveoli (Order1) is about 4mm / sec. The R.B.C. pass in a single file in the pulmonary capillary and spend 1-2 seconds thus following enough time for gas exchange.

The pulmonary vascular resistance is increased when there is a reduction in number or calibre of pulmonary vascular bed as in diffuse interstitial pulmonary

fibrosis, extensive lung resection, multiple emboli and destruction of vascular bed. Hypoxia can cause active pulmonary vasoconstriction and thus increase the resistance.

Ventilation Perfusion Relationship

Hypoxemia with normocapnia is frequently seen in acute severe asthma in humans.[23] Arterial hypoxemia is probably due to regional ventilation-perfusion abnormalities, since arterial carbon dioxide tension is normal and arterial oxygen tension increases appropriatly when animals are ventilated with oxygen.

Ideally the ventilation and perfusion to a lung unit should be well matched for optimal exchange of gases. In the erect human lung at rest the ventilation per unit volume per unit time is greater at bases than at apices. Similarly the blood flow is greater at bases than at apices. But the reduction in perfusion from base to apex is greater than the reduction in ventilation. Because of this, the ratio of ventilation (V) to perfusion (Q) varies in different lungs units.

Thus the ventilation/ perfusion ratio at lung base is below 0.5 and at apices approaches 2.

The overall ventilation of the lung is 4 liters and perfusion is 5 liters per minute giving a ratio of 0.8.

This overall effect maintains an arterial PO_2 of 96mm of Hg and pco_2 of 40mm hg.

In disease states, if ventilation and perfusion to the same lung unit are equally reduced there will not be, much alteration in blood gases. But if only one component is affected more severely the blood gases will become abnormal especially with regard to oxygen. Thus if the alveoli are ventilated and not perfused the unit acts as a dead space (as in pulmonary embolism). On the other hand if the alveoli are not

ventilated but perfused the unit acts as a right to left shunt (as in pneumonia, atelectasis etc). In chronic Bronchitis there is regional mismatch leading to derangements in blood gases. In asthma and emphysema there is also a mismatch of ventilation to perfusion resulting in hypoxia. But here co_2 retention is uncommon because of hyperventilation[23].

Blood Gas Transport

The oxygen in blood is carried in two forms. Arterial blood contains 19.8 ml of oxygen per 100ml of which 19.5ml is carried in combination with Hemoglobin as oxyhaemoglobin and 0.3 ml in dissolved form. The maximum amount of oxygen that can combine with Hemoglobin is 1.34 ml per 1 gram of Hemoglobin. Thus the fully oxygenated arterial blood is 97.5% saturated and has partial pressure of oxygen (PAO_2) of 95mm of Hg.

Hemoglobin demonstrates a variable affinity towards O_2, the relationship between saturation and partial pressure assuming a sigmoid curve.

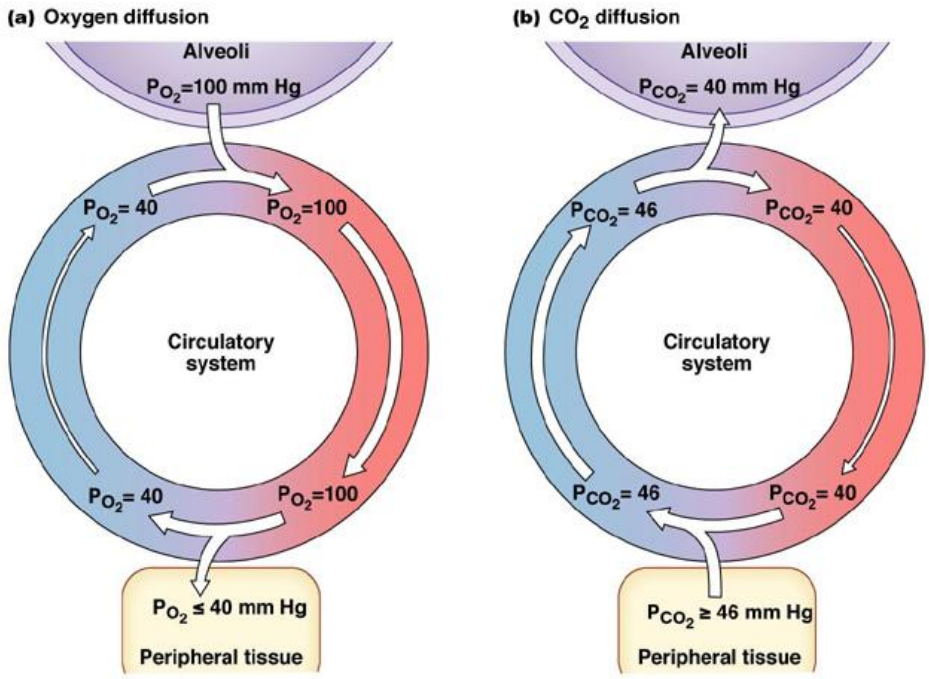


Figure 8. Blood Gas Transport

Because of the shape of the curve, at low PO_2 the oxygen up take is more than compared to that of higher PO_2.

A change in affinity between 0_2 and Hemoglobin causes a shift in the position of the curve. If the curve shifts to right as in fever, acidosis, increase in PCO_2 etc the affinity is decreased and 0_2 is released easily. A shift to left as occurred in low PCO_2, hypothermia etc. The affinity is increased and more oxygen is taken up. Nevertheless there may be a real depression of ventilator drives as assessed by the mouth occlusion technique in rapid eye movement sleep[24]

The Bohrs effect is the CO_2 induced shifts in the curve. This is physiologically suitable in that shift to left increases 20 uptake in lungs and a shift to right in tissues increases the releases of oxygen.

Carbon Dioxide Transport

The CO_2 produced in tissues is transported for excretion, to the lungs, in 3 forms: dissolved, as bicarbonate and in combination with Hemoglobin as carbaminohaemoglobin. The mixed venous blood has 53.1 ml as carbamino compound as 3.0ml in dissolved form.

In the tissues the CO_2 diffuses into blood and enters into R.B.C. in the RBC, it is hydrated to form carbonic acid.

$$CO_2 + H_2O \xrightarrow{C.A} H_2C0_3$$

This carbonic acid immediately dissociates to from $HCO_3 + H$

$$H_2CO_3 \longrightarrow HCO_3 + H$$

The HCO_3 diffuses out of RBC into plasma and an ion of Chloride moves into to maintain electrical equilibrium (Chloride shift). The H^+ is mopped up by the reduced hemoglobin.

This process is reversed in the lungs and CO_2 diffuses out along the pressure gradient.

The CO_2 equilibrium curve is nearly linear in the physiological range of 40-50mm Hg.

The curve shows a shift to left in tissues, that is deoxygenated hemoglobin takes up more CO_2 and in lungs it shifts to right in lungs liberating CO_2. This is called the Haldane effect.

Arterial Blood Gases

The final common pathways of gas exchange after ventilation, distribution, diffusion and perfusion is the arterial blood. The arterial PO_2, PCO_2 and pH reflect the adequacy of gas exchange.

No one single pattern of Pao_2 , $PaCo_2$ and PH is characteristic of severe asthma. Several Experimental and clinical studies have demonstrated dissociation between maximal expiratory airflow rates and pulmonary gas exchange in both acute and chronic forms of bronchial asthma.[25]

Hypocapnoea is said to be present when P_ACO_2 falls below 36mm Hg . This is seen in hyperventilation due to anxiety, metabolic acidosis, exercise etc.

Hypercapoea is present when P_ACO_2 is greater than 44 mmHg. It is the result of alveolar hypoventilation due to central causes, pulmonary parenchymal or thoracic cage disorders.

The normal arterial pH is a 7.4 a pH below 7.36 shows acidosis. In respiratory acidosis the $PaCO_2$ is elevated with an elevation of serum bicarbonate due to renal compensation. In metabolic acidosis (diabetes mellitus) the serum bicarbonate is reduced primarily and P_aCO_2.falls due to attempted respiratory compensation. When pH exceeds. 7.44. Alkalosis is present. Respiratory alkalosis is seen in alveolar hyperventilation resulting in a fall of P_aCO_2. In metabolic alkalosis there is an increased serum bicarbonate.

Hypoxaemia is a fall in P_aO_2. There are 4 basic physiologic mechanisms for hypoxaemia, alveolar hypoventilation, right to left shunting, alveolar capillary block and ventilation perfusion imbalance.

Pulmonary Function Tests

The pulmonary function tests are not diagnostic of any specific lung disease, but they play an important role in diagnosis of the nature and extent of respiratory defect. They are useful in helping to select the most specific effective therapy, in judging the effectiveness of pulmonary therapy, in assessing patients pre-operatively, in assessing disability, and in monitoring and treating patients in respiratory failure.

Measurement of Static Volume And Capacities:

Spirometry is a simple investigation which gives useful information regarding both static and dynamic volumes of lung. By spirometry all volumes except RV and all capacities expect FRC and TLC can be measured. The requirement consists of water or dry spirometer attached to a kymograph and plots gas volume breathed (in liters) on the vertical axis versus time (in seconds) on the horizontal axis. Electronic spirometers measure similar parameters via parameters via pressure volume transducers.

The RV, FRC, and TLC cannot be measured directly from spirometer. Usually FRC is measured by either dilution or washout of an inert gas like Nitrogen, Neon or Helium. RV is derived from this by subtracting ERV from FRC and TLC is derived by adding VC or RV. The open circuit method of measuring FRC uses nitrogen. Here the patient breaths 100 % O2 for 7 minutes and all expired gas is collected. Since all nitrogen in expired gas has come from the functional residual gas in lungs, FRC can be calculated using the formula[26].

$$FRC = \frac{(a - b) \times V}{b}$$

In these measurements, if the patient is connected to the spirometer at resting and expiration, FRC is measured. If the patient is connected at end of forced expiration RV can be measured and if he is connected at deep inspiration TLC can be measured.

FRC and TLC can also be measured by whole body plethysmography. The FRC and TLC measured by dilution and plethysmography are virtually indentical in normal subjects. But in chronic obstructive lung diseases and bullous diseases the gas dilution or wash out techniques tend to under estimate theses volume since they may not dilute or washout the trapped air. In this circumstance plethysmography gives more accurate measurements.[26]

TLC can also be calculated by suing Posterio anterior and lateral radiographs of chest by suing Bernhard's method. The radiographic volume thus measured volume thus measured correlates well with that measured by plethysmograph both in normals and in patients with chronic obstructive lung diseases.[19]

Measurement of Compliance:

Static Compliance*:*

The pressure changes (P) are measured by a manometer attached to a tube leading to a thin walled baloon which is swallowed to the midesophagus. The volumes changes (V) are measured while patient, breaths into a spirometer. The measurements are made at static conditions – that is, when there is a no air flow- and compliance is calculated.

Dynamic Compliance:

Using same equipment measurements are made at end – inspiration and end – expiration when patient is continuously breathing at different frequencies. Compliance at different frequencies are calculated.

Dynamic Properties:

Airway resistance can be measured in directly by studying the airflow rates during forced vital capacity manoeurs. Velocity of expiratory airflow is maximal at higher lung volumes when airways diameters are largest. Air velocity decreases as air is exhaled from a full lung (TLC) to Residual volume. Therefore the initial slope of the expiratory curve is steeper than the slope of middle or final portions. The initial part also is effort dependent and later part is effort independent.

The Timed Vital Capacities:

This is the volume of gas expired when the patient breaths out as rapidly as he can after a deep inspiration per given time. This can be recorded on the revolving drum of spirometer. The time factor usually given is 0.75 second. 1/ second and 3 seconds and are called forced expiratory volumes in 0.75 sec, 1 second 3 sec respectively ($FEV_{0.75}$, FEV_1, and FEV_3).[25]

Normal persons can be exhaled approximately 83% of V.C. in 1.0 sec and 97% of VC in 3.0 seconds. There rates tend to diminish slightly with age, lower values indicate significant airway obstruction. The values are near normal in restrictive diseases. Normal values do not exclude early obstruction in small airways.[26]

Forced expiratory time:

This is the minimum time in seconds required for the subject to expire the entire FC. This is normally less than 4 seconds. It is increased in patients with airway resistance.

Maximum expiratory flow rate:

(Forced Expiratory Flow-FEF 200-1200)

This is the mean forced expiratory flow measured between the first 200 ml and 1200 ml of forced vital capacity.[26]

Peak Expiratory Flow Rate (PEFR):

This is the maximum airflow maintained for about 10 mili second. In the initial part of forced expiration. This measurement is made using the Wright's peak flow meter or the De Bono whistle. These two parameters (PEF 200-1200 and PEFR) estimate the airflow resistance in the earlier, effort dependent portion of expiration, They are reduced in severe airway obstruction. Thus they do not give more information than that can be obtained from FEV_1.

Figure 9. WRIGHT'S PEFR - Meter

Maximum Mid- Expiratory Flow Rate (MMFR):

(Forced Mid – Expiratory Flow :FEV 25 – 75%)

This is the mean expiratory flow during the middle half of the forced expiratory vital capacity maneuver. This parameter measures the flow in the effort independent part of expiration. As the lung volume decreases the diameter of peripheral small airway decreases slowing airflow rates in the middle and terminal portion of flow curve. This slowing is greater with damage to the small airways. As in smokers with early Emphysema and in patient with viral bronchiolitis or asthma. This it can be used as a screening test in detecting small airways obstruction.[27]

Flow Volume Loop

This is probably more sensitive in detecting early small airways obstruction than conventional volume time spirography. Here the volume in liters as measured by waterless wedge spirometer, is plotted against airflow rates measured by electrical transducers. The patient breaths quietly inscribing a tidal volume loop. Next he inhales fully to total lung capacity and then exhales as rapidly and as completely as possible to his residual volume and then inhales fully again. The maneuver first inscribes the expiratory loop and is followed by the inspiratory loop. From this flow loop the following data are obtained: VC, FEV, maximum expiratory and inspiratory flow (V_{max}) and expiratory flow rates at 50% and 75 % of VC (V_{max} 50 and V_{max}75). [27]

Reduction of all airflow rates occurs in moderate or severe obstructive airway diseases.

In mild obstruction due to any causes (early Emphysema, mild Asthma) the flow volume loop shows a characteristic expiratory dip. There is also a reduction in

$V_{max}50$ and $V_{max}75$ disproportionate to reduction in V implying a reduction in maximum mid-expiratory flow rate.

Restrictive lung disorders will show decreased VC with airflows appropriate to the lower lung volumes. Upper airways obstruction gives characteristic loops.

Maximum Voluntary Ventilation (mvv):

There is the maximum volume of gas which can be breathed per minute. It provides a good overall assessment of the entire respiratory apparatus since it represents the final common pathway of ventilation. Usually the gas breathed with maximum effort for 15 seconds is collected in a Doughlas Bag and multiplied by 4 to give M.V.V. Indirectly M.V.V. can be calculated by multiplying FEV_1(obtained by spirometry) by 37. The values of MVV correlate well with clinical dyspnoea.[27]

Air Velocity Index (AVI):

This is the ratio of percent predicted MVV to the percent predicted V.C. usually it is 1 ± 0.2. It is the less than 0.7, MVV has suffered more than V.C. and indicates obstructive lung lesion. Values of 1.3 or more indicate a restrictive lesion since the V.C. is affected more, with near normal MVV.

Nitrogen Wash Out:

Normally all the nitrogen in the lungs can be washed out in 7 minutes by breathing pure oxygen. The nitrogen in the expired alveolar gas is estimated after 7 minutes of breathing pure oxygen (alveolar gas is taken as that part of the gas expired between 750ml and 1250 ml of expired gas). If this concentration is more than 2.5% it indicates that there are hypoventillated alveoli which still contain high

concentration of Nitrogen even after 7 minutes, i.e... That there is mal- distribution of inspired gases.[29]

Closing Volume:

Normally at low lung volumes (at RV) the airways in the upper zones are patent and in the dependant lower zones are closed. This is due to difference in pleural pressure from top to bottom of lung in erect position.

During inspiration the initial part of inspired gas passes into upper zones and later part to lower zones. During expiration the lower zones empty first and as RV is approached they start closing due to increasing pleural pressure around them. The upper zone empty last. The volume at which the airways start closing is called closing volume.

It is sensitive test in measuring maldistribution of inspired air and in small airway disease. The subject inhales from RV gas air containing a bolus of about 50 ml of traces gas (Xenon, Argon). He inspires slowly till TLC and then expires slowly to RV. The concentration of Tracer gas during this expiration is continuously measured and plotted against volume expired.[28]

The curve obtained typically shows 4 phases. The I phase contains dead space gas with no trace gas. II phase contain mixed dead space and alveolar gas, III phase contains alveolar gas and IV phase contains gas from those areas which received more tracer gas as they were at lower lung volumes. The transition between phase III and IV is taken as the point at which airways are losing. From this point to RV is the closing volume.

In normal young adults in sitting posture it is about 40% of TLC: i.e. the airway start closing at lung volumes below 40% of TLC.

An increase in closing volume implies premature airway collapse as occurs in Emphysema, chronic bronchitis, Asthma, Mitral stenosis etc.

Though closing volume is valuable in detecting early small airway disease, it becomes unmeasured when the airway obstruction becomes gross. Thus if FEV is abnormal, closing volume cannot be measured. The other tests available to measure unevenness of ventilation include tests using Radio-active gases by rebreathing techniques and by estimation of dynamic compliance.[28]

Diffusing capacity:

Carbon monoxide is usually used to measure this since its diffusion throughout the physiological media resembles that of O_2.

There are two main groups of methods for the estimation of CO diffusing capacity. The steady state method in which the uptake of CO and the alveolar tensions are measured over a period of several minutes and a single breath method in which the rate of uptake and the alveolar tension are calculated from the change in composition of a gas mixture containing CO which is inspired, held in lungs for 10 seconds and then expired.[29]

The measurements made in both methods are:

(i) Volume of CO taken up

(ii) Alveolar Pressure of CO

(iii) Mean capillary pressure of CO.

The steady state method is more accurate and is used for detailed physiologic studies, the single breath is quicker and adequate for screening studies.

Measurment of Perfusion:

This are not usually performed in routine practice. The pulmonary pressure can be measured by cardiac catheterisation. By advancing the catheter and wedging it in the smallest radicle of pulmonary artery, wedge pressure is measured.

The distribution of blood in pulmonary vascular tree is estimated by Radio-Isotope techniques. Using Xenon or Albumin macroaggregates labeled with I 131 Xenon 133 is dissolved in saline and injected intravenously and radio-activity counted by external counters. The macroaggregates of I131 labeled albumin get impacted temporarily in a small number of precapillary pulmonary blood vessels when injected intravenously. This allows the external counters to count the radioactivity is each lung zone.[30]

The Xenon131 study by intravenous administration also helps measuring pulmonary blood flow. Pulmonary blood flow can be measured using the direct Fick method:

$$\text{BLOOD FLOW (l/min)} = \frac{O_2\text{uptake ml/min}}{\text{(Arterial-venous) } O_2 \text{ difference ml/l.}}$$

Measurment of Shunts:

Right to left shunts produce venous admixture effect and can results in arterial hypoxaemia. The percentage of cardiac output that is shunted across the pulmonary circulation can be estimated by breathing 100% .O_2 and measuring the alveolar arterial PO_2 difference . This difference is 15 mm Hg per every 1% shunt while breathing 100% O_2. Thus estimating the exact alveolar arterial PO_2 difference while breathing 100% O_2will help to compute the exact percent of shunt. Normally there is an anatomical shunt of about 4% of cardiac output.[31]

Measurment of Blood Gasses and PH:

Oxygen:

(i) Van Slyke Manometric Method:

This measures the saturation of oxygen. It is based upon the principle that O_2 is absorbed by sodium hydrosulfite.

(ii) Oxygen Electrodes:

This measures the partial pressure of O_2. It is based that electrical current can flow from a silver reference electrode in the presence of oxygen.

(iii)Ear Oximeter:

This also measures O_2 saturation. It is not a sensitive method.

CARBON DIOXIDE:

This can be measured by:

I. Van Slyke manometric method which is based on the principle that CO_2 is absorbed by sodium hydroxide.

II. Glass electrode which measures the partial pressure (PCO_2).

III. Indirectly by using Henderson-Hasselbach's equation after measuring pH and plasmic bicarbonate.

$$PH = 6.1 + \log \frac{HCO_3}{0.03 \quad PaCO_3}$$

IV. Mixed venous PCO_2 can be measured by employing the Campbells rebreathing method.

P H:

The arterial pH is measured by-

i) Electrode.

ii) By using Henderson –Hasselbach equation if plasma CO2 content and pressure are known.

The arterial sample of blood is obtained from readily accessible artery like the radial for measurement of arterial blood gases and PH.[31]

PATHOGENESIS

The main reason for the occurrence of bronchial asthma is the non-specific hyperirritability of the tracheobronchial tree. So when airway reactivity is high, the response in the form of bronchospasm will be more. The diurnal fluctuation in the lung function is also important in the occurrence of night attacks and early morning dipping.

This airway responsiveness can be increased by (1) Allergens like oxidant air pollutants Eg. Ozone, nitrogen dioxide and (2) Viral infections of the respiratory tracts.

The exact cause for this airway hyper responsiveness is not known. Lot of postulates are there like airway inflammation Evidenced from the broncho alveolar lavage (BAL) study and endobrochial biopsy study.

Another hypothesis is the interaction between resident and infiltrating inflammatory cells like mast cells, eoinophills, macrophages, and lymphocytes. And releases mediators of inflammation like – histamine, bradykinin, leukotrienes C, D & E, platelet activating factors , prostaglandins (PGs) E_2, F_2 and D_2– produce an intense immediate inflammatory reaction causing bronchoconstriction, vascular congestion and mucosal edema. Also cause increase mucus production and impaired mucociliary transport.

The eosinophilic proteins like major basic protein and eosinophilic cationic protein airway epithelium and these epithelium will be sloughed into the bronchial lumen forming creola bodies aggravating the inflammation of the bronchial tree and bronchial obstruction by these Creola bodies.

T-Lymphocytes and its subclass like T_{111}, T_{112} Facilitates granule release from basophils and aggravate asthma response.

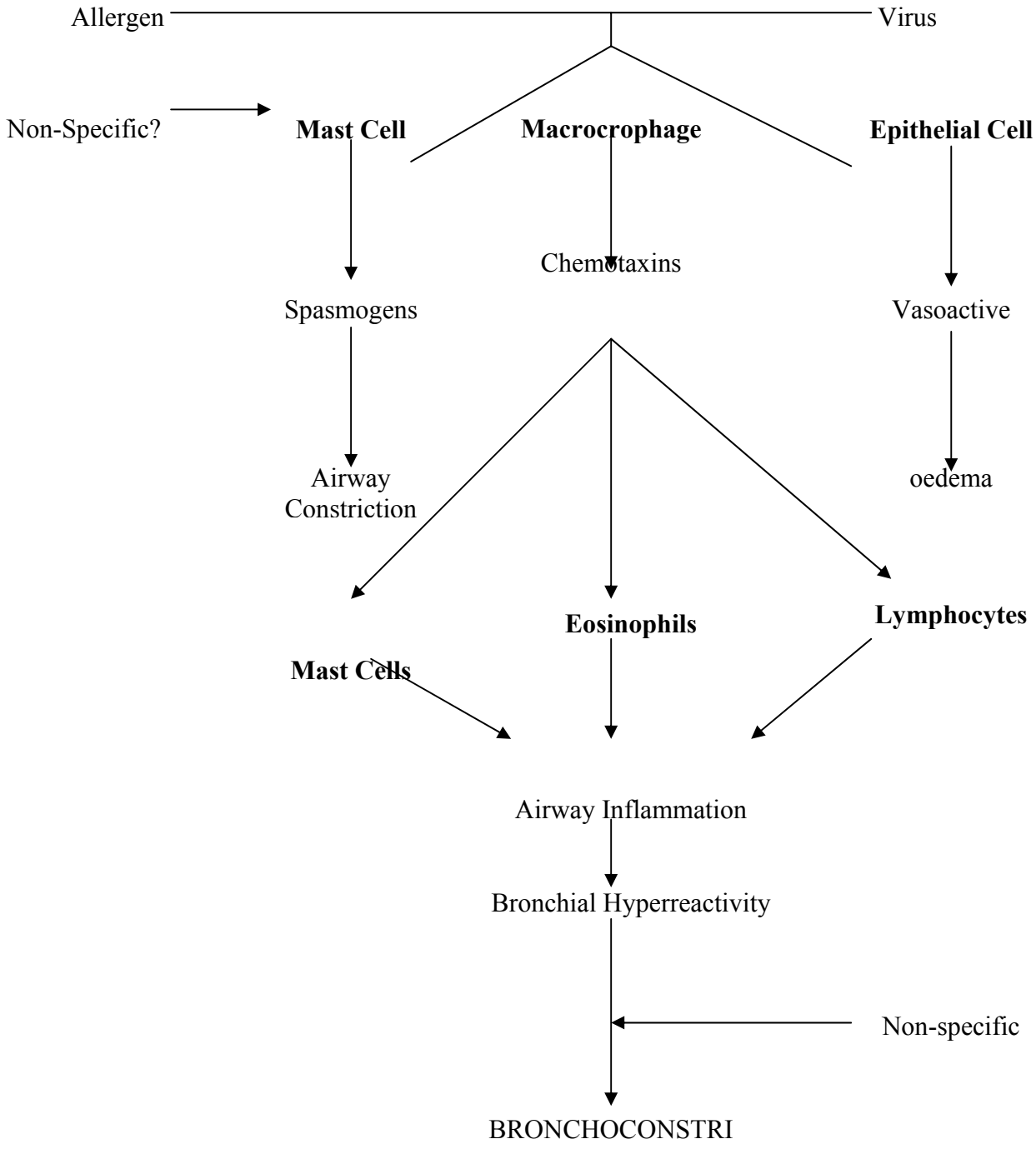


Figure. 10 Revised view of Asthma

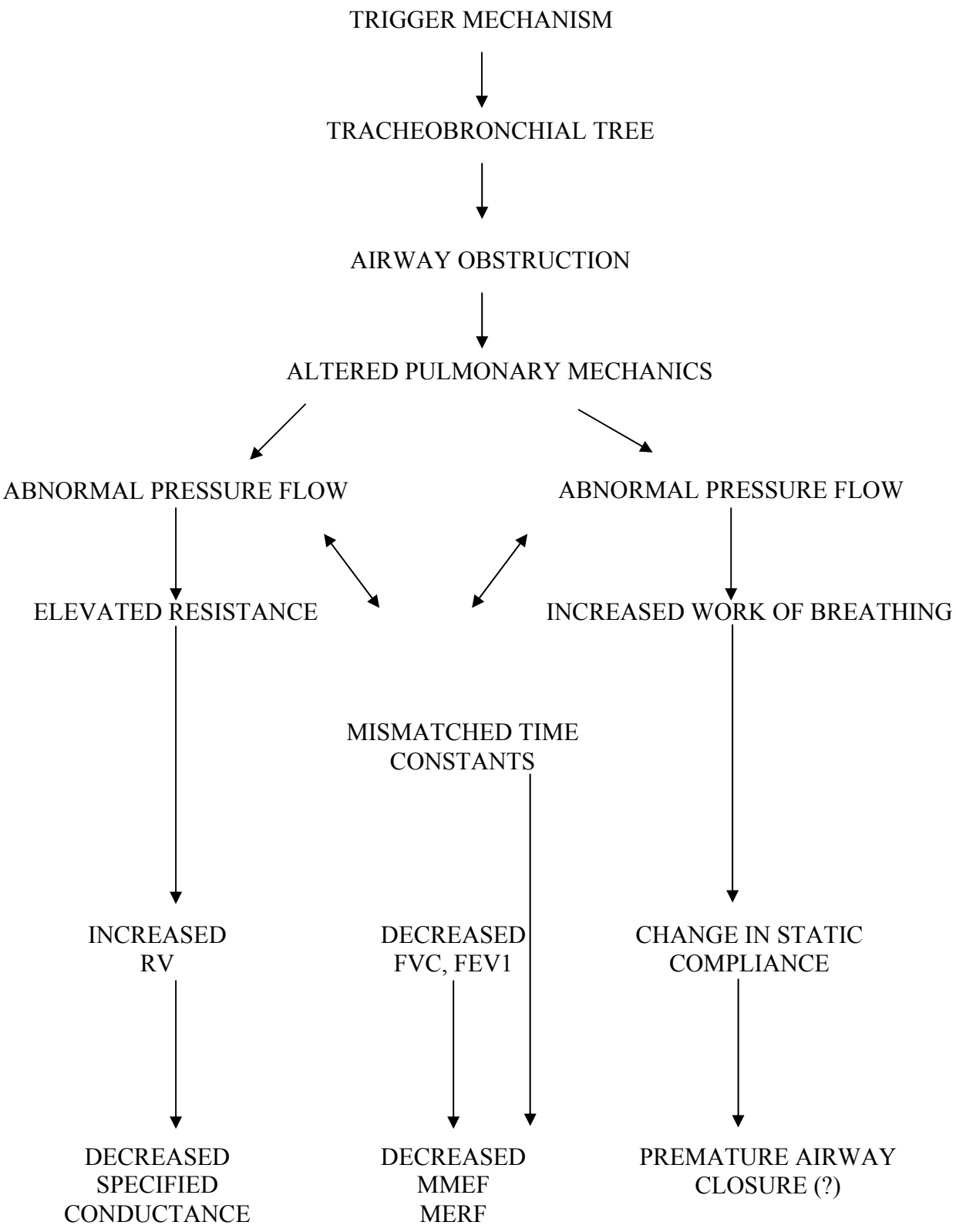


Figure 11. SCHEME OF THE FUNCTIONAL DEFECTS SEEN IN ASTHMA

Allergic Asthma

Mainly by IgE response. IgE antibodies to the air borne allergens will be already formed and remained attached to the mast cells. So exposure to same allergen will cause attachment of the allergic antigen to the IgE antibodies already attached to the mast cells, and cause degranulation of mast cells. And the mediators of the inflammation like histamine, bradykinins will be released and cause inflammation of the tracheobronchial tree, bronchospasm , musosal edema and thus genesis of asthma.

Nitrogen dioxide is also an irritant gas and even short term exposure to concentrations as low as 1.5ppm increases bronchial reactivity in normal subject.[32]

Drug Induced Asthma

Drugs like aspirin, tartrazine (colouring agent), B-adrenergic anatagonists and sulfating agents can cause asthma. And drug induced asthma has got great morbidity. Usually begins with perennial vasomotor rhinitis and associated ocular and nasal congestion and broncho spasm.

ENVIRONMENT AND AIR-POLLUTION CAUSING ASTHMA

Heavily industrialized and densely populated Urban Areas are notorius in causing asthma. Air pollutants like Ozone, Nitrogen Dioxide and Sulphur Dioxide are important in causing bronchospasm. Also climatic conditions which promote the concentration of atmospheric pollutants (like winter) and antigens (like flowering seasons of certain plants) are also notorious in precipitating Asthma.

Occupational Asthma

The diagnosis of occupational asthma is suggested by the onset of a wheezing in a pollution for which there is a clear industrial exposure.[33]

Exposure to:-

(1) Metal salts like Platinum, Chrome and Nickel.

(2) Wood and vegetable dusts like those of oak western red cedar grain, flour, castor bean, green coffee, bean etc.

(3) Pharmaceutical agents Like Antibiotics , Piderazine , Cimetidine

(4) Industrial Chemical & Plastics.

(5) Biologic enzymes like laundry detergents.

(6) Animal and insect dusts, serums and secretions. Can cause bronchospasm

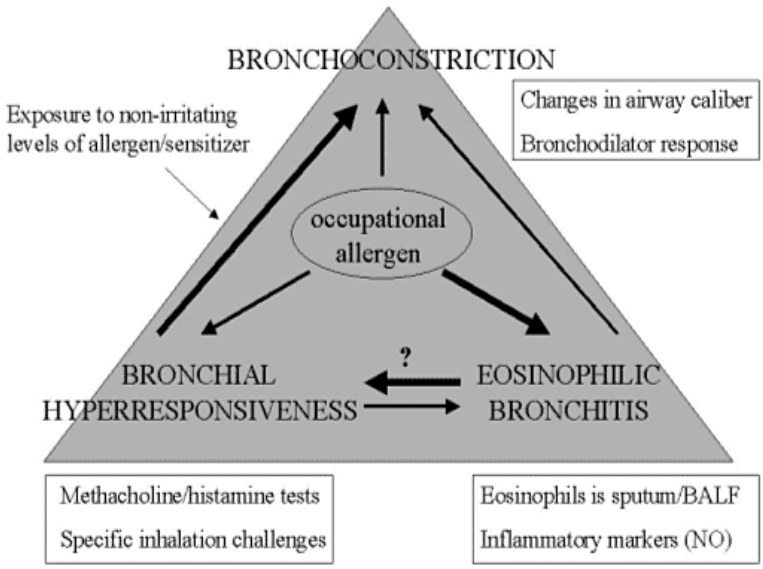


Figure 12 Occupational allergy

Mechanism of Bronchopasm Are:-

a) By formation of specific IgE.

b) Substance causes direct liberation of broncho constrictor substances .

c) Or substance may cause direct or reflex stimulation of airways in asthmatics.

Infection Induced Asthma

Viruses causing respiratory infections are notorious in causing asthma. Like in infants respiratory syncytial virus and parainfluenza viruses and in older children and in adults rhino virus and influenza viruses.

Exercise Induced Asthma

Here exercise is the only triggering factor for the production of asthma, though exercise may produce bronchospasm to some extent in all asthmatics.

Causes of the exercise induced asthma may be:-

(a) Inhalation of cold air – will enhance the tracheo – bronchial response

(b) Thermally induced hyperemia and engorgement of microvasculature of bronchial wall, which does not appear to involve smooth muscle contraction.

Emotional Stress Induced Asthma

Psychological factors can provoke asthmatic diseases. This may be affected through modification of vagal efferent activity.

PATHOLOGY & CYTOLOGY OF ASTHMA

In the normal human bronchial epithelium, four main cell types are most often seen, which all rest on a basement membrane (Rhodin, 1974; Heino,1987) (1) Ciliated cells (2) Basal cells (3) Secretory cells (Mucous or Goblet) and (4) Kultschitsky (Neuroendocrine, Amine containing, Apud or K) cells. There are roughly 3-5 ciliated cells for every mucous cell (Rhodin, 1974; Mc Dowell et al, 1978). As many as 10 ciliated cells to one goblet cell in the normal human air – way epithelium have been described (Soderberg et al; 1990). A prominent feature described is a marked airway edema with the separation of the epithelial cells, leaving in many areas only a layer of basal or reserve cells (Dunnill, 1960).

The shedding of the airway columnar epithelial cells is commonly attributed to asthma. This epithelial shedding is due to edema formation and plasma exudation (persson-1986).

Other less specific changes in asthmatic air-way epithelium are goblet cell hyperplasia and epithelial cell metaplasia.

In our recent studies of bronchial biopsies from newly diagnosed asthmatics, showed different kinds of airway epithelial changes has already been occured early in the disease process. For instance, epithelium contains increased number of inflammatory cells; goblet cells hyperplasia with or without ciliated cells; and there is squamous metaplasia and shedding of the epithelium (Liatinen. L.A.,Laitinen, A and Haahtela T, Unpublished Observations). Goblet cell hyperplasia, which has also been described in chronic bronchitis, may reflect, a common non–specific reaction of the air-way epithelium to an irritant (Mc Dowell and Beals, 1987).

Changes in inflammatory cell counts in the airway epithelium.

(a) Mast Cells.

The regular occurrence of mast cells in the air-way epithelium, even in mild asthmatics, supports the idea that these cells may be important in the initial stage of asthma. (Salvoto, 1968; Laitinen and Laitinen, 1988). Also broncho alveolar lavage (BAL) studies have shown significant increase in the percentage of mast cells in asthmatics when compared with healthy controls (Wardlaw et al. 1988)

(b) Eosinophils.

Its has been know for more than 80 years that bronchial asthma is associated with eosinophilia of the blood and lungs (Ellis, 1908). Respiratory epithelial damage, is the main pathogenesis for bronchial asthma, is due to the toxic protein released from the eosinophilic granules (Gleich et al, 1975; Frigas et al, 1981; Venge et al, 1987). The three main toxic proteins in the eosinophilic granules are; eosinophil derived neurotoxin (Durack et al 1981), eosinophil cation protein (Venge et al 1980), and eosinophil peroxidase (Carlson et al 1985). In addition, eosinophils release other mediators such as leukotriene C_4 (Weller et al, 1983) and Platelet Activating Factor (Lee et al 1984). In bronchial biopsies, increase in the number of the eosinophils in the bronchial mucosa has been related to the deterioration of the asthma symptoms (Laitinen et al 1991).

(c) NEUTROPHILS

Neutrophils have been associated with acute (transient) bronchial hyper-responsiveness in many studies (Nadel , 1984; Boushey and Holtzmann, 1985) according to Holtzmann et al .(1983), neutrophils are active participants in epithelial damage.

The presence of a few neutrophils in the epithelium is probably a normal phenomenon because neutrophils may be found even in the lavage fluid of normal subjects (Crystal et al 1986). Neutrophils number were even more numerous in the control specimens in a recent biopsy study in the mild asthmatics (Beasley et al 1989).

Bronchial mucosal cytology during an asthma attack.

The broncho-alveolar lavage (BAL) study during the asthma attack shows increase in eosinophils and a close relationship exists between peripheral eosinophilia and bronchial hyper responsiveness (Wardlaw et al 1988; Frigas and Gleich, 1986).

After epithelial cell detachment, the basal or reserve cells that are left on the basement membrane may serve as a source where regeneration of bronchial mucosa occurs. Metaplastic epithelium of the simple stratified non-ciliated variety exhibiting mitoses has been described in asthmatic subjects (Dunnill, 1982).

In the airways the epithelial basal cells and / or mucous cells proliferate in response to injury causing marked increase in the mitotic rate, goblet cell hyperplasia, stratification and non-cornifying and cornifying epidermoid metaplasia (squamous).This sort of loss of ciliated cells is an early response to many forms of injury (Keenan et al, 1982; Mc Dowell and Beals, 1987).

Airway smooth muscle hypertrophy and/or Hyperplasia has been described in asthmatics (Dunnill et al, 1969; Takizawa and Thurlbeck, 1971; Heard and Hassain, 1973).

The intercellular junctions between endothelial cells in the postcapillary venules are loosely organized . This loose arrangements of the endothelial cell junctions may contribute to make these vessels more susceptible to the effects of various kinds of inflammatory mediators by facilitating the separation of the adjacent endothelial cells.

The endothelium of the bronchial postcapillary venules in asthmatics has wide interrupted gaps (Laitinen and Laitinen, 1990). This gap formation may be relevant in the pathogenesis of asthma. The possible increase in plasma exudation may be an important contributing factor to the epithelial shedding process and to the development of the inflammatory cell influx in the mucosa in asthma.

Asthmatics with severe symptoms can show the features of the classical inflammatory reaction in the airways; destruction of the tissue; vascular permeability changes with edema formation and inflammatory cell influx. Airway epithelial damage may be the initial or the end stage stimulus for the increased bronchial responsiveness. When, why and how the disease in the airways proceed to the condition of a fully developed probably irreversible inflammatory reaction, eg with intense eosinophilia, mucous plugging and edema , as seen in autopsy, is not known. Morphological studies will give important information about changes in the airways underlying the functional abnormalities in asthma. Recent biopsy studies have revealed that in asthma an airway inflammatory process is present even at a clinically early stage of the disease. This inflammatory response shows a particular cellular

picture with concomitant vascular changes. So far we do not know what the stimulus for the reaction is and why asthmatic subject develop the inflammatory response.

The importance of tumour necrosis factor in bronchial asthma has been elaborated in detail in the editorial of the Indian journal of the chest disease 1995. They had done a lot of studies on bronchial asthma patient with fiberoptic bronchoscopy as the main tool. And they used modern cellular and molecular biological techniques for studying the airways of living asthmatics. These studies showed that chronic airway inflammation is the cause for bronchial asthma orchestrated predominantly by the T-Lymphocytes by upregulating mast cell and eosinophil function.[34] These are the main cells involved in the inflammatory response. This is achieved through release of messengers called as cytokines. These cytokines are increased in bronchial asthma and play a pivotal role in the inflammatory response. The cytokines can activate host defense mechanism or paradoxically can also promote immunopathological processes.[35]

TNF-α Plays a major role in airway-inflammation in bronchial asthma. It is evidenced in two studies like, TNF – α levels in sputum and bronchoalveolar lavage (BAL) fluid were reported to be increased in asthmatic patients[36] .Immuno-histochemical studies of bronchial biopsy of asthma have detected seven fold increase in TNF-α in mast cells, in the submucosa of asthmatic subjects.[36] This TNF-α is responsible for the transendothelial migration of inflammatory cells; chemoattraction for neutrophils and monocytes and transepithelial migration of neutrophils through production of IL-8 [34,43,].

Thus new methods of treatment of bronchial asthma could probably be evolved by interfering with the cytokine network.

Types of Asthma

1. Extrinsic asthma (atopic asthma, IgE mediated asthma)
2. Intrinsic asthma (idiopathic or cryptogenic asthma)

I. Extrinsic Asthma (Atopic Asthma, IgE Mediated Asthma)

This type of asthma will have a hereditary predisposition. And usually associated with allergic conditions like allergic rhinitis and atopic dermatitis and attacks will be usually seasonal.

II. Intrinsic Asthma (Idiopathic or Cryptogenic Asthma)

There will not be any family or personal history of atopic diseases. Serum IgE levels will be normal. Usually starts late in the life.

Grading Of Bronchial Asthma

Mainly 3 types of asthma.

I. **Episodic asthma:-** Occurred as Paroxysms in between patient will be completely asymptomatic.

II. **Severe acute asthma:-** Acute life threatening attacks of asthma also called as "Status Asthmaticus".

III. **Chronic persistent asthma:-** again subdivided into 3.

(a) Mild persistent asthma.

- Asthma symptoms>1 Time/Week<1Time / Day.
- Affect activity and sleep.
- Night attacks > 2/ Months.
- PEF OR FEV > 80% Predicted.
- Variability 20-30%.

(b) Moderate persistent asthma.

- Asthma symptoms daily.
- Affect activity & sleep.
- Night attacks > 1/Week
- Daily use of short acting B agonist inhaler.
- PEF or FEV > 60% < 80% predicted.
- Variability > 30 %

(c) Severe Persistent Asthma.

- Continuous symptoms.
- Frequent exacerbations.
- Night attacks frequent.
- Activities limited
- PEF OR FEV1< 60% predicted
- Variability >30%.

CLINICAL FEATURES

Symptoms of asthma consists of triad of dyspnoea, cough and wheezing. It will be occurring as paroxysms or episodes, that means in between the attacks patient will be completely asymptomatic and during the asthma attacks patient will experience a sense of chest constriction, with non- productive cough. Respiration becomes harsh and wheeze will be audible in both inspiration and expiration, expiration becomes prolonged, with tachypnoea , tachycardia and mild systolic hypertension . The lungs become over inflated and the anteroposterior diameter of the thorax increases. Accessory muscles of respiration become active and paradoxical pulse often develops. (These two signs will give the idea of severity of asthma).

Coughing out of thick stringy mucus, often takes the shapes of casts of distal airways, called Curshmans spirals.

One of the common feature is development or worsening of symptoms at night .It is known that both normal people and asthmatic patients have circadian rhythm of peak expiratory flow rate (PEFR)[38]; (PEFR) is lowest between 3am and 6 am. As a result, it is common for patients to wake in the early morning with symptoms of asthma.[39] Rarely, asthma presents as cor pulmonale. [40] They have airflow obstruction for long enough to get chronic pulumonary hypertension and right sided heart failure.

In extreme situation, wheezing may lessen or even disappear and cough becomes extremely ineffective and respiration becomes just like gasping. This will be due to extensive mucus plugging and impending suffocation. In such condition positive pressure ventilation with endotracheal intubation may be required.

INVESTIGATION & DIAGNOSIS OF BRONCHIAL ASTHMA

Routine Blood Examination; - Eosinophilia-5-15% of total leucocyte count.

SPUTUM EXAMINATION; - X-Ray chest – to rule out complications like chest infections, rib fracture, pneumothorax and pnemomediastinum.

Arterial Blood Gas Analysis:- To assess the severity of the disease. Initially there will be respiratory alkalosis and hypocarbia, later stages respiratory acidosis and hypercapina.

Pulmonary Function Tests:- To assess the obstruction and response to treatment . During the acute attack the dynamic lung volumes are reduced with a decrease in the forced Vital Capacity (FVC) , Peal Expiratory Flow rate (PEFR), and Forced Expiratory Volume in one second (FEV). The FEV/FVC ratio is usually less than 75%. These parameters improve by 15% or more in response to a broncho dialator.

Static lung volume also show changes like increase in Total Lung Capacity (TLC) and Residual Volume (RV). The ratio of RV/ TLC increases owing to air trapping.

Studies of lung volume mechanics show a decrease in frequency dependent compliance, increase in airway resistance and decrease in specific airway conductance. The diffusing (DLCO) is preserved.

The progress of asthmatics can be followed easily by serial recording of Peak Expiratory Flow Rate (PEFR) or Forced Expiratory Volume in one second (FEVI). These simple tests give a good objective assessment of the severity of the attack and response to therapy. Asthma may worsen insidiously without much clinical

symptoms, so serial recording of PEFR will give an early warning of an impending acute attack of asthma.

Immunological Tests

It is necessary to investigate for provocative allergen. This is by allergen challenge tests: - by skin prick with common air bone allergen and house dusts. Another method of allergen challenge is by nebulised aerosols of extracts of suspect materials and measuring the response over PEFR assessments. This test is useful only in a small percentage of extrinsic variety of asthmatics.

Diagnosis of bronchial asthma.

The diagnosis of asthma is made on the basis of a compatible clinical history of paroxysms of cough, breathlessness and wheezing plus a demonstration of variable air flow obstruction , which may classically be seen as' Morning dipping' of the PEFR .[41]

Making a diagnosis of asthma.

>15% improvement in FEV_1 or PEFR following administration of a bronchodialator or >15% spontaneous change in PEF or FEV_1 during one week of home monitoring.

DIFERENTIAL DIAGNOSIS

a. Upper airway obstruction by tumour or laryngeal oedema.

But here patient will have stridor and harsh respiratory sounds which will be localized to the trachea. Diffuse wheezing will be absent (which is a characteristic of bronchial asthma). If presentation is not typical, challenge testing is indicated.[42]

In general, however in establishing the diagnosis of asthma the physician is confronted with differential diagnosis of wheezing, dyspnoea perhaps cough.[43]

b. Glottic dysfunction

Unlike asthma, arterial oxygen tension will be well preserved here.

c. Endo bronchial diseases

Foreign body aspiration	– History will be suggestive.
Neoplasm	–Wheezing will be localized.
Bronchial stenosis	– Localised Wheezing.

d. Acute Left Ventricular Failure

Moist Basilar rales, gallop rhythms, pink frothy sputum and other signs of heart failure.

Pulmonary Embolism – In recent review, 5000,000 patients per year have a deep venous thrombosis, 10 percent of whom develop pulmonary Embolism.[44]

e. Recurrent episodes of bronchospasm

Carcinoid tumor –Episodes of other allergic manifestations.

Recurrent pulmonary emboli –Pulmonary angiography & Lung Scans are confirmatory.

Chronic bronchitis – There won't be true symptom free period.

f. Eosinophilic pneumonias.

Chemical pneumonias

Cocaine toxicity[45,46]

Exposure to insecticides and cholinergic drugs.

Acquired immune deficiency Syndrome; wheezing and chest tightness common with AIDS population.[47]

TREATMENT OF BRONCHIAL ASTHMA

COMES UNDER 3 MAJOR HEADINGS.

(1) Patient Education [51]

- Understanding asthma
- Understanding the medications
- Technical aspects of medication
- Goal of treatment
- Early recognition of exacerbations
- Early (self – administered) treatment of exacerbations
- Home monitoring of Peak Expiratory Flow
- Action plan

(2) Environmental Control[50,51]

- Sensitizers
- Bronchospastic triggers
- Medications / chemicals.

(3) Pharmacotherapy

- Inhaled B-2 Agonists
- Inhaled corticosteroids
- Ingested corticosteroids
- Others

Understanding Asthma[51]

Basic Knowledge of physiology of asthma like – airway inflammation and bronchoconstriction, airway inflammation inducers, broncho constriction triggers should be taught to the patient. It is useful for the management of asthma.

Understanding The Medications

Teach the patient about the vast number of asthma medications and the use of confusing devices. Also instruct them the difference between bronchodilators (symptom relievers), and anti inflammatories (preventers). Importance of regular use, common side effects of the medications and the ways to prevent or minimize these side effects also should be instructed. Like candidiasis in case of inhaled steroid can be prevented by rinsing mouth after inhalation of steroid.

Action Plan

A card booklet containing instructions regarding.

- Symptoms
- Medication
- PEF assessment
- When & what to start.

Methods for achieving patient education by:-

- Asthma camps
- Asthma education by non-physician medical personnel, office nurse or technician.
- Booklets / pamphlets

- Video tapes
- Audio tapes.

Environmental control

Sensitizing agents

Identification of the sensitizers mainly through history in home, work, school, recreational activities, churches etc. Allergen – challenge by skin prick test is also useful. And avoidance of the allergens as far as possible.

Bronchospastic Triggers.[51]

Avoidance of triggers like exercise, cold air and inhaled irritants (by wearing a mask or a scarf over the face while exposing to cold air or irritants).

Medications and other Chemicals[50]

Avoid drugs causing bronchospasm like NSAIDS, ASA, Beta-Blockers, Food additives, Avoid insect bites, Insect stings.

PHARMACO THERAPY

Drugs used in bronchial asthma.

1. **Broncho Dialators.**[50]

(a) Sympathomimetics:- Adrenaline, Ephidrine, Isoprenaline, Orciprenaline, Salbutamol, Salmeterol.

(b) Methyle Xanthines: - Theophylline, Aminophylline.

(c) Anticholinergics :- Atropine methonitrate, Ipratropium bromide .

2. **Mast cell stabilizers.**

   Sodium Chromoglycate, Nedocromil, Ketotifen

3. **Corticosteroids**

(a) Systemic – Hydrocortisone, Prednisolone.

(b) Inhalational – Beclomathasone Dipropionate, Fluticasone.

4. **Miscellaneous**[51]

- Mepyramine and congeners (Anti Histamines)
- Anti Leukotriens –Zafirlukast.

Now pharmaco therapy is limited to three classes of drugs.

Inhaled B-2 agonists

Inhaled corticosteroids

Ingested corticosteroids

First line is inhaled B2- agonist usually short acting. If night attacks and early morning dipping present , start long acting B-2 agonist like salmeterol and steroid inhalers. Steroid inhaler dose can be adjusted in a step up or step down manner. If asthma symptoms are continuing even after maximum dose of inhaled steroid, start a brief course of oral steroid.

In exercise induced asthma Sodium Chromoglycate and Nedocromil can be used – but for exercise induced asthma, long acting B-2 agonist like salmeterol are more effective. Inhaled anticholinergics are also useful. If all these measures fail refer the patient to centers undertaking trials of Methotrexate, and Cyclosporine for asthma management.

Antibiotics like macrolides are rarely useful because rarely mycoplasma infection may affect asthma patients.

The National Institute Of Health:-

Global Initiative For Asthma – Had advocated a long term management regimen of asthma. Daily medications required to maintain control of asthma.

(a) Mild persistent asthma.

- One daily controller medication.
- Anti- inflammatory (steroid) inhalation
- Long acting B-2 agonist inhalation (Especially for night attacks)

(b) Moderate persistent asthma.

- Daily controller medication
- Corticosteroid inhaler
- Long acting B-2 agonist inhalation (Especially for night attacks)

(c) Severe persistent asthma.

- Multiple daily controller medications
- High doses of corticosteroid inhalation.
- Long acting B-2 agonist inhalation
- Long term oral corticosteroid.

Prognosis & clinical course.

- Mortality rate from asthma is small
- 5000 deaths/ year of population of 10 million patients at risk.

Clinical course of asthma.

- 50-80% -Have good prognosis.
- Asthma is not progressive
- Spontaneous remissions in 20% of cases
- Good improvement in 40% of cases.

Complication of Bronchial Asthma

(a) Acute severe asthma (Status Asthmaticus)

(b) Spontaneous pneumothorax & / or

(c) Pneumomediastinum.

Acute Severe Asthma (STATUS ASTHMATICUS)

Reversible branchoconstriction is the hallmark of asthma. Intense inflammatory responses that contribute to airway caliber narrowing and occlusion[48] may be coupled with the inhalation of allergens and other irritants that provoke asthma to stimulate cough receptors and induces coughing.[49]

American thoracic society has defined status asthmaticus as an acute asthma in which the degree of bronchial obstruction is either severe from the beginning or increases in severity and is not relieved by the usual treatment. Manifested clinically by persistent dyspnoea, prolonged expiratory wheezing, tachycardia, use of accessory muscles of respiration and cyanosis. Associated findings are:- spirometric, arterial blood gas analysis shows severe hypoxemia academia and / or hyper – carbia.[52]

However asthma occasionally develops unexpectedly and cataclysmally over a short period of time , giving rise to the need for immediate intubation, ventilatory support or even causing death within a few minutes of onset.[53]

Management of Acute Severe Asthma

1. Oxygen.

Ventilation – perfusion mismatching may cause hypoxemia , so PAO_2 decreases . So Oxygen should be given in a nasal cannula at 4-6 liters / minute or with a close fitting mask.

Arterial blood gas analysis is important PA CO_2 40 mm Hg is a sign of status asthmaticus

2. Intravenous fluids.

- Correct dehydration
- Maintain an IV line
- Avoid volume overload (Especially in elderly)

3. Special medications.

(a) Sympathomimetics.

- Repeat nebulizers of selective B-2 agonists OR
- Subcutaneous injection of 0.3 ML of 1:1000 Epinephrine (Look for Cardiac side effects) [50]

(b) Corticosteroids.

Early oral or IV corticosteroids (particularly hydrocortisone – onset of action is early[44] .

(c) Theophylline Compounds

- IV Aminophylline – It improves diaphragmatic muscle function and improves broncho dilatation
- 0.6 mg/ Kg slowly over a period of 20-30 mts.
- Maintainance 0.5 mg / Kg / mt.

(d) Anti Cholinergics

- Ipratropium bromide.

(e) Electrolyte

- Sodium Bicarbonate – If pH valve < 7.2
- Potassium chloride 2-3 mEq /Kg/ Day in Potassium lost Patients.

(f) Antibiotics

- Usually viral infections – do not require antibiotics.
- Rarely secondary infections (discoloured mucus, fever cough, pulmonary or paranasal sinus involvement) better use antibiotics.

Need For Hospitalisation Depends On

- Minimum response to treatment in first 1-2 hour.
- Presence of complications like cardiac arrhythmia, pneumonia, pneumothorax .

Assisted Ventilation

If

- $PaCO_2$ > 50 mm of Hg.
- PaO_2 < 50 mm of Hg.

Those require early endotracheal intubation

(If positive pressure ventilation is required > 24 hours, tracheostomy is required)

- For spontaneous preumothorax and/ or pneumomediastinum should be treated with inter costal drainage.

MAGNESIUM

Magnesium is the fourth most abundant and important cat-ion in humans. It is extremely essential for life and is present as intracellular ion in all living cells and tissues. Adult body contains 20g of magnesium, 70%of which is found in bones in combination of calcium and phosphorus 30% in soft tissues and body fluids. [54,55]

Sources:

Magnesium is widely distributed in vegetables, found in porphyrin group of chlorophyll of vegetable cells and also found in almost all animal tissues, other important sources are – cereals, beans, green vegetables, potatoes, almonds and dairy products. Eg: cheese, cereals, nuts beans vegetables (Cabbage, cauliflower) meat, milk, fruits. [56,57]

Distribution: Total body magnesium is approximately 2400 m Eq. Approximately 2/3 occurs in bones, 1% E.C. fluid and remainders in soft tissues. [58,59]

Dietary Requirements: Adult man – 350mg/ day,

Adult women – 300mg/ day.

Plasma Levels: 1.5 to 1.8 mEq/L, which is rigorously maintained within normal limits. 15% of total body magnesium is exchangeable with the tissues but there is wide variations. Muscle contains 20% of exchangeable Mg and bone only 2% of hyperthyroidism markedly increases the amount of exchangeable Mg, where as it is reverse in hypothyroidism.

Blood: Magnesium exists in blood partly bound to proteins. Under conditions of physiological PH roughly 1/3 rd is protein bound and remainder 2/3 is ionic.

C.S.Fluid: Concentration of Mg in C.S. Fluid is ½ as high as in plasma.

Absorption: Average daily intake in humans is 250-300mg, much of which is obtained from green vegetables where Magnesium is found in porphyrin group of chlorophyll. Roughly 1/3 of dietary Mg is absorbed; the remainder is passively excreted in faeces. Absorption takes place primarily in small bowel, begining within hour after ingestion and continues at a steady rate for 2 to 8 hours by that time 80% of total absorption has taken place.[53,54]

Factors affecting absorption:

Size of Mg load:

Absorption is doubled when normal dietary Mg requirements is doubled and vice versa.

Dietary Calcium:

Increased absorption in calcium deficient diets. Decreased absorption occurs in presence of excess of Ca. A common transport mechanism from intestinal tract for both Ca and Mg is suggested. [62,63]

Motility and Mucosal State:

This also affects absorption. In hurried bowel, absorption is decreased. Absorption decreases in damaged mucosal state.

Vit-D: Helps in increased absorption.

Paratharmone: Increases absorption.

Growth hormone: Increases absorption.

Other factors:

High protein intake and Neomycin therapy increases absorption.

Fatty acids, phytates and phosphates decreases absorption.

Excretion:

Magnesium is lost from the body in faeces, sweat and urine 60 to 80% of orally taken Mg is lost in faces.

Sweat Loss:

Currently it is drawing attention, 0.75 mEq of Mg is lost daily in perspiration with normal health and with normal diet. Loss is much increased with visible frank sweating.

Urine:

Regulation of magnesium balance is principally dependent on renal handling of the ion. In a normal healthy adult with normal diet 3 to 17mEq are excreted daily.

Factors affecting Renal Excretion:

Calcium intake: increased dietary calcium produced increases excretion of Magnesium.

Paratharmone (PTH) diminishes excretion. [64]

Antidiuretic harmone (ADH): Increases Mg excretion

Growth Harmone (GH): also increases excretion Magnesium.

Aldosterone increases excretion.

Thyroid harmones: 80% greater excretion in hyperthyroidism.

Alcohol ingestion: Oral ingestion of as little as 1.0 ml of 95% alcohol per kg, increases urinary excretion 2 to 3 fold. The increased excretion primarily accounts for Mg-deficiency in chronic alcoholics with Delirium tremors.

Administration of acidifying substances (NH_4cl) is followed by increased urinary elimination of Magnesium.

Functions:

1. Role in Enzyme action[64] :

Magnesium is involved as a cofactor and as an activation to wide spectrum of enzyme actions. It is essential for peptidases, ribonucleases, glycolytic enzymes and co-carboxylation reactions.[65]

2. **Neuromuscular Irritability:**

Magnesium exerts an effect on neuromuscular irritability similar to that of ca^{++}, high levels depress nerve conduction and low levels may produce tetany (hypomagnesemic tetany)

3. As constituent of Bones and Teeth. About 70% of body magnesium is present as appetites in bones, dental enamel and dentition.

Plasma Mg in Diseases:

a) Hypermagnesemia: Raised values have been reported in

uncontrolled diabetes mellitus, Adrenocortical insufficiency, hypothyroidism, advanced renal failure and Acute Renal failure.[66]

b) Hypomagnesemia: Low values are observed in Malabsorption Syndromes and Kwarshiorkor, prolonged starvation, prolonged gastric secretion, Hyperthyroidism, portal cirrhosis, prolonged use of diuretics, chronic alcoholism, delirium tremons, renal diseases, primary aldosteronism. Low levels of magnesium seen in uremia, rickets and abdominal pregnancy.

Magnesium Deficiency:

In man, 'Overt' magnesium deficiency rarely occurs.

In animals, 2 types;

Unsupplemented whole milk (in calves)

Endemic disease: Class called as "Grass" staggers (Or Grass Tetany) cattle's grazing in fields fertilized with nitrates condition occurs due to high NH_3 content of diet. Absorption of Magnesium is impaired by the formation of insoluble ammonium-magnesium-phosphates.

Clinical feature:

Restlessness and convulsions followed by death.

In humans:

Experimentally induced prolonged Magnesium-depletion reported in two patients (Reported by Shils) Both were fed Magnesium-deficient synthetic diets: one for 274 days and another for 414 days. In both, plasma Magnesium fell slowly over several months.

Clinical Features:

Personality changes, gastrointestinal disturbances, gross tremours, hyporeflexia, abnormal eletromyograph, +ve chevostek's sign, epileptic form

convulsions. Both cases, despite adequate Calcium and potassium intake, developed hypocalcemia and hypokalaemia.[67,68]

Biochemical functions:

1. Magnesium is required for the formation of bones and teeth.
2. Magnesium seems as a cofactor for several enzymes requiring ATP.

   Eg: Hexokinase, Glucokinase, Phosphofructokinase adenylate cyclase.

Determination of Serum Magnesium[68]

Early, outdated methods involved removal of calcium and precipitation of magnesium as the phosphate or 8-hydroxy quinoline complex before determination, sometimes by complexometric titration. Alternatively, the latter complex was measured fluorimetrically in ethanolic solution. Colorimetric study methods used the coloured magnesium complexes of titer yellow or methyl thymol blue. Emission flame photometry was also tried.

Currently atomic absorption photometry is the method of choice and the only other method in common use is the colorimetric one using cities the Mann-Yoc dye or more often, calmagite (1-azonapthlalene-3sulphonic acid (1-2 methylebenzene) now popular for both automated and manual use. Recently, Tobata et al (1985) described a reaction rate method based on the activation of hexokinase by magnesium ions. They linked this via glucose-6phosphate dehydrogenase to an NADPH reaction and measured the production of NADPH at 340nm. Good correlation with atomic absorption valves was claimed for this method[68].

Atomic Absorption Method:

The average between-batch precision for the manual technique is 0.06 mmol/ltr.

Measurement can be performed using isotope dilution mass spectrometry and Cali et al (1973) developed on atomic absorption reference method, based on that of Pybus et al (1970) developed, which they assured against the isotype technique. An independent assessment was performed and some revision suggested by Pickup et al (1974). This reference method was not intended to be suitable for the control material and as a method against which others could be compared.

For routine use, many atomic absorption methods have been described. Specimens diluted with lanthanum chloride solution are sprayed directly into an air-acetylene flame with modern instruments a dilution of 1 in 50 usually affords adequate sensitivity and resonance lines at 422.7nm for calcium and 225nm for magnesium are obtained[68].

Calorimetric method using calmagite

(Gindler and Heth, 1971, Khayman – Basli et al 1977)

Magnesium reacts with the blue dye, calmagite, in akaline solution to form a red complex. Protein interference and dye precipitation are avoided by including the 9-ethylene-oxide adduct of P-nonyl phenol (Bion NEq) and polyvinyl Pyrolidone (Bionpvp) calcium interference is avoided by preferential combination with EGTA and heavy metal interference is prevented by cyanide.[69]

Reagents:

1. **Dye reagent:** this contains 60mg calmagite, 20g potassium chloride, 1.08g Bion Neg and 10g Bian pvp per liter. It is obtainable ready prepared as magnesium rapid state dye reagant (Product no.) 455084; pierce chemical co) and is stable at the room temperature for 2 yrs.

2. **Base reagent**: this contains 2g potassium cyanide, 15.8g potassium hydroxide and 450mg EGTA per liter. It is obtainable ready prepared as magnesium rapid state base reagent (Product no 455043, pierce chemical Ca) and is stable at room temperature for 2 yrs.

3. **Working reagent:** prepare freshly each day by mixing a volume of reagent (2) with 10 volumes of regent (1). The mixture is stable for 24hrs.

4. Standard magnesium solution, 10mmol/l for the stock solution dissolve 2.003g $mgcl_2$, $6H_2O$ or 2.463 g mgso4, $7H_2o$ in water and make to a liter.

5. Working standards, l and 3 mmol/1. dilute the stock standard 1 to 10 and 3 to 10.

Technique: Place 50ml serum in a test tube and add 5ml working reagent. Similarly treat 50ml of the standards mix and allow to stand for 20 min before reading the spectrophotometer of 532nm using the working reagent as blank. The colour is stable for several hours. Beers low is obeyed up to at least 2mmol/1.

Calculation:

$$\text{Serum Magnesium (mmol/1)} = \frac{\text{Reading of unknown}}{\text{Reading of lower standard}} \times 1.0$$

Interpretation:

Normal ranges for serum magnesium are rather dependent on the method of analysis but 0.7 to 1.0mmol/1 is appropriate for atomic absorption methods. [70]

Increased serum magnesium concentration can occur in the oliguric phase of acute renal failure, in dehydration and in chronic renal failure. In these circumstances, it behaves in a similar way to potassium and this is also seen in Addisons diseases and during the development of diabetic ketoacidosis. Hypermagnesemia is associated with depression of central and peripheral nervous activity.

Magnesium deficiency is usually associated with low serum magnesium levels. It can occur because of impaired intake, increased faecal loss, increased urinary loss, or altered balance between intra cellular and extracellular fluids. The last is seen during insulin treatment of diabetic ketoacidosis. It may be a factor in causing a slight reduction of serum Magnesium in diabetic subjects compared with non diabetics but there is no difference in tissue magnesium levels (Levin et al 1981).

Hypomagnesemia may be accompanied by tetany, unrelieved by calcium administration, by muscle twitching and tremors with mental irritability, hallucinations and aggressiveness (as in delirium tremens) by convulsions and by eventual death if severe. It also causes hypocalcmia unsponsive to PTH or vitamin D but corrected by magnesium replenishment, which also corrects the other manifestations. Nephrocalcinosis with possible progressive renal damage so occurs[70].

Impaired intake of magnesium is seen especially in kwarshiorkar, to some extent in alcoholism, and in prolonged intravenous nutrition without magnesium supplements. Increased faecal losses, usually accompanied by diminished urinary magnesium excretion, occur in malabsportion and steatorrhoea, in persistent diarrhea,

vomiting or gastric suction, and in some cases of laxative abuse or ingestion of increased amount of calcium salts[60].

Renal losses, normally about 5mmol/24hrs, when increased may be considered under several headings.

1. Inherited tubular disorders may involve magnesium alone but more often are associated with impaired handling of potassium or hydrogen ion as in renal tubular acidosis.
2. Hormonal influences are seen in primary hyperaldosteronism with concomittent potassium loss, in bootters syndrome and in some cases of hyperthyroidism.
3. Tubular cell damage leading to impaired conservation is associated with aminoglycoside (Eg: gentamycin) and cisplatin therapy losses also occur during the diuretic phase of acute renal failure.
4. Decreased reabsorption affecting magnesium and potassium is seen in prolonged diuretic therapy and is sometimes important in patients coming to open heart surgery.
5. Increased filtered load with appropriate increased renal excretion occurs following tissue mobilization as in starvation, injury, early diabetic ketoacidosis and acute pancreatitis. Mobilization from bone occurs in primary hyperparathyroidism but this usually matches the increased renal excretion and hypomagnesaemia is uncommon. This may occur, however after removal of the adenoma and be associated with refractory hypocalaemia which only disappears after treatment of the magnesium deficiency. Hypomagnesemic may be factor in post-operative tetany in these patients.[53]

Role of Magnesium in Asthma:

A growing body of evidence suggests that Magnesium deficiency contributes to exacerbations of asthma and as a control that Magnesium useful in alleviating bronchospasm in these patients. Although the precise mechanism is unknown, it has been suggested that magnesium plays or role in the maintenance of airway patency via relaxation of bronchial smooth muscle is a relaxing factor of airway smooth muscles regulates bronchial tone, competes with Calcium influx by blocking voltage dependent calcium channels, inhibits intracellular Calcium release from sarcoplasmic reticulum and is associated with airway hypersensitivity.[70]

Stabilization of mast cells and manifestation of wheeze and impairment of lung function, is seen.[72] Also, it has some influence and inhibits the cholinergic transmission. Stimulatory synthesis of nitric oxide and prostacyclin. Magnesium sulfate improves lung function and causes bronchodilatation. Magnesium deficiency has several effects on asthma and its clinical presentations. Low serum Magnesium level causes increased hospitalization. It is mast cell stabilizer and results in bronchoconstriction due to increasing airway hyperactivity and hyper responsivness through increased acetylcholine production at cholinergic nerve endings and improves pulmonary functions.[73]

Serum Magnesium level comprises only 1% of total body content, studies have disclosed no correlation between intracellular content of magnesium and serum levels and signs of hypomagnesemia may be seen in normal or minimally low serum Magnesium concentrations. This finding is important from the therapeutic point of view and suggests adding Magnesium supplements to asthmatic patients diet.[74]

Medications that are prescribed in asthma like anti-inflammatory agents-Glucocorticoids and bronchodilator agents, and patients receiving these drugs for long

time cause depletion of Magnesium in humans through intracellular shift and urinary excretion.[75]

The potential role of dietary intake of Magnesium has been recognized in Magnesium levels. Low dietary intake of Magnesium is associated with impaired lung function,bronchial hyperreactivity and wheezing. chlorophyll is the Magnesium chelate of porphyrin in green leafy vegetables, legumes and nuts are the excellent and richest dietary sources of Magnesium vitamin D and metabolites enhance Magnesium absorption by the distal bowel.[76]

Low Magnesium value was found in 47.3% of females which is higher than in males

Since asthma is one of the most common chronic diseases world wide, with up to 150 million people currently suffering the disease. Further, this has been climbing steadily since 1950's. In the last 10 yrs asthma cases have risen 50% globally. Magnesium is involved in numerous biochemical and physiological processes that directly influence the lung function and indirectly influence respiratory symptoms.[77] The mechanisms underlying the effects on lung function and symptoms include alteration of smooth muscle function, neuromuscular excitability, immune function, oxidative stress, DNA and RNA synthesis, and Enzymatic activity.[78]

Epidemiological evidence from population-based study indicates that low dietary intake of magnesium is associated with increased incidence of asthmatic symptoms, wheezing, reduced lung function, and lower lung volume and flows. It appears reasonable to assume therefore, magnesium status may be a causal factor in asthma.[79]

Immunochemical properties of antigens that cause atopic diseases.

Antigens that induce allergic responses of the immediate type catopyl are called atopic allergens. It is generally accepted that atopic allergy in people is primarily mediated by allergen specific IgE antibodies.[80] It is known that the synthesis of both IgE and IgG_4 is stimulated by the lymphokine interleukine 4 (IL-4) and is inhibited by the lymphokine interferon-gamma (IKN-) [81].

The common environmental sources of allergens include pollens from different weeds, grasses and trees, molds, animal danders, insect venoms, mites, reactive chemicals, such as some drugs or industrial substances can also be allergens following their conjugation with body proteins or other macromolecules. Under natural condition of exposure, a person becomes sensitized on absorption of minute quantities of allergens.

Each environmental source contains multiple allergens on the basis of their relative allergenic activities, the allergens can be divided into major and minor ones. Major allergens are highly active in the majority of allergic individuals tested, while the minor ones are weakly active[82].

Individuals may vary not only in their responses to different allergens but also in their responses to the different antigenic determinants (Epitope) of the same allergen molecule. For example, studies with clinically modified derivatives of the major bee venom allergen phospholipase suggests that persons who are allergic to bee venom produce IgE antibodies specific for distant regions of phospholipases. This variation in responses of individuals to different allergens or their determinants is believed to be genetically determined. It has been shown by studies that an individuals sensitivity to an allergen is correlated with their major histocompatibility complex (MHC) product[82].

Bio chemical Studies of Allergens:

Some of the allergens have been isolated and characterized most of these allergens were purified by standard technique use of gel filtration and ion-exchange chromatography, and in some cases, by affinity chromotography on immunosorbents containing monoclonal antibiodies. [83]

The most widely used in vitro tests are the radiodergosorbent test (RAST) and Crossed radioimmunoelectrophoresis (CRIE) for measuring the reaction of allergens with their specific IgE antibodies. A recent advance is to immunoscreen the allergens (s) of interest complementary DNA (CDNA) expression libraries with human IgE antibodies.[84]

Some of the allergens have enzymatic activities but others have as yet unidentified biochemical functions. The aminoacid sequences of nearly all allergens are known. This is in large measure due to advance in cloning and sequencing techniques of molecular biology in recent years.

The complete conformational structure of most proteins are not known since they can be determined only by x-ray crystallography and/ or by nuclear magnetic resonance spectroscopy. In some cases they can be obtained from molecular modelling studies when the confirmational structure of closely related protein is known.[85]

Immunologic Studies of Allergens

A knowledge of the conformational structure of allergens is required for understanding their antibody combining sites. These sites are also designated as B-cell epitopes since antibodies are the receptor molecules of B-Lymphocytes. Most allergens listed show greatly reduced antibody binding activities on denaturation, for example, required allergens, group 1 mite allergens and bee venom phospholipase.[83,84]

These results indicate that their B-cell epitopes are mainly of the topographic type consisting of discontinuous segments of the polypeptide chain. But allergens also have B-cell epitopes of continuous segments of polypeptide chain, for example, the grass pollen group I allergens, the allergens from cod fish and midge.

A recent report indicates that the oligosaccharide side chain of bee venom phospholipase A_2 is a B-cell epitope for IgE antibodies in bee venom allergic patients.

T cell epitopes of several allergens have been studied. More allergens were studied in human-T-cell lines, and one T cell epitope was identified to have the same sequence as that of residue 80 -108 of rat olph2-cuglobulin.[85] Proliferation assays with human peripheral blood lymphocytes demonstrated that patients have a varying pattern of recognition of T-cell peptides of csit I but one peptide, residue 98-111 was using new strains of different haplotypes, T-cell epitopes of the following allergens were mapped; ragweed allergen Amba III, a bee venom allergens phospholipase. Apim I and melittin Apim III and hornet venom allergens Dol m v.

The B and T cell epitopes of an allergens may or may not represent separate regions of the molecule. For ex. One of the B-cell epitopes of this is located in residue 91-101 and one of its T-cell epitopes is located in the overlapping region of residue 98-111.But the B and T cell epitopes of melittin do not occupy overlapping regions, as they are located in radius 11-19 and 19-26 respectively. Analogs of melittin, which differ only in the region of B-cell epitope, elicited analogue specific IgE and IgG responses in responder strains of mice, thus providing direct experimental support for the T-cell control of the B-cell response[85].

IgE Biology:

The discovery of IgE is by Istizaka and colleagues over 25yrs ago initiated to modern era of allergey research by providing a focus for the study of allergic phenomenon. Induced IgE is primarily regarded as an agent of disease rather than a functionary in the immunologic network of disease prevention. However with attention focused on the "Adverse" effects of IgE, it should be mentioned that this class of immunoglobulins has been implicated in immunologically beneficial role. Pathways that involve IgE have been demonstrated to be cytotoxic for parasites, and IgE was recently shown to be central molecule in providing protective immunity against these infections. [88]

Properties of IgE: Kinetics

IgE exhibits second features that distinguish it from other immunoglobulins. The normal plasma IgE concentration acin nanogram range (50-300ng/ml). Immunisation with an appropriate antigen causes levels of IgE to increase 3 to 12 fold the majority of which is antigen specific. In contrast IgG exhibits only a marginal increase in plasma levels after antigen stimulation and only a fraction of that is antigen specific. Moreover, IgE levels decrease rapidly following antigen challenge because of a short serum half-life (2.5days) and efficient episilon-specific regulatory mechanisms. IgG concentrations are more stable owing to their 20 to 25 day half life cellular Interactions of IgE[84,85].

IgE receptors and other IgE binding proteins.

A number of proteins capable of binding IgE have been identified. These include two distinct cellular receptors, the high-affinity and the low-affinity Fc

receptors for IgE, and a variety of IgE-binding factors including, epsilon binding protein and the truncated soluble fragments.[88]

Other IgE-binding proteins:

In addition to cellular membrane several IgE binding factors have been identified. Epsilon-binding proteins was initially characterized because it adhered to an IgE sephorse column. Subsequent molecular studies reaveled epsilon-binding protein to be a ubiquitous mammalian lectin that interacts with the carbohydrate moieties of IgE.[88] Both its function and the significance of its IgE binding are unknown. Recent evidence suggests that lectin may act as a cell-adhesion protein on the surface of mast cells and macrophages. Molecular studies on another type of IgE binding factor revealed striking structural.

MATERIALS AND METHOD

It is case control study to ascertain serum magnesium levels in children attending **B.L.D.E.U'S Shri .B .M. Patil Medical College Hospital and Research center Bijapur**, with different grades of asthma and acute exacerbation.

Source of data:

All the pediatric cases of bronchial asthma attending the out patient department of pediatrics and admitted to pediatrics ward at **B.L.D.E.U's Shri B.M.Patil Medical College**, Hospital & Research Centre, Bijapur-586103.

Duration : From 1st Nov 2008 to 31st March 2010.

Method of collection of Data:

After taking written informed consent and fulfilling inclusion criteria children in the age group 3 to 14 yrs will be included in the study.

Method of study:

1. Detailed data will be taken to grade asthma as mild intermittent, mild persistent, moderate persistent and severe persistent.

2. Respiratory rate , duration of wheeze, accessory muscle used will be used to grade acute exacerbation as mild, moderate and severe.

3. Detailed general and systemic examination will be done for the purpose of exclusion.

4. Serum magnesium level will be estimated

Sample size;

Sample size of 40 patients are required for the study.

Statistical data

$$N = \frac{t^2 s^2}{E^2}$$

E= 0.0516

S ≡ 0.14 (Variation in the measurements of serum magnesium levels[6])

T = 2.33 (Standard Distribution[6])

N = 39.68 ≡ 40

Statistical analysis:

1. Computation of mean ± standard deviation for serum magnesium levels.
2. T-test to be used for comparison of serum magnesium levels between male and female children in asthmatic groups.
3. T-t statistic which helps to associate a degree of confidence to observe in sample size of female children in asthmatic groups.
4. E- Permissible error taken up by investigator to assess difference between true mean and sample mean.
5. S^2 - Average deviation of serum magnesium level in asthmatics from average serum magnesium levels.

METHOD OF ESTIMATION OF SERUM MAGNESIUM:

It is enzymatic end point method. Principle of reaction is that the calagmite combines with the magnesium to form a complex which is measured at 520 nm. Reagent is in liquid form.

A magnesium standard is provided with the reagent.

Wavelength	:	520 nm.
Temperature	:	37 degree Celsius
Cuvette	:	10 nm path length
Incubation	:	5 minutes
Standard	:	2mg/dl

Selection criteria

Inclusion criteria:

Children between age group 3 to 14 yrs. All diagnosed patients with history of asthma with or without acute exacerbation.

Exclusion Criteria

1. Age less than 3 yrs and more than 14 yrs
2. All patients with other respiratory illness other than asthma and with lower respiratory tract infection.
3. Patients with acquired and Congenital heart diseases.
4. Patients with renal diseases.
5. Patients with Malabsorption syndrome.

6. Patients on drugs like Diuretics, Vitamin D, Calcium antagonist, Digoxin, Laxatives.
7. Patients with Diabetes mellitus.
8. Patients with signs of primary magnesium deficiency.

RESULTS

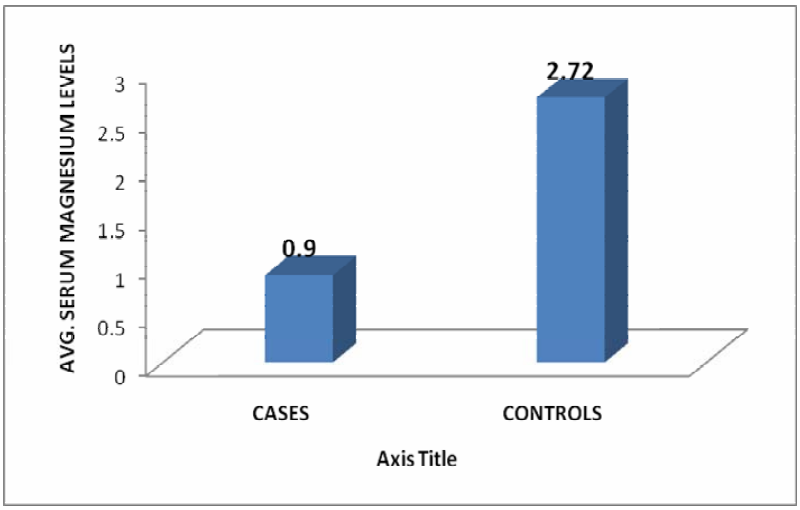
The present study conducted at department of pediatrics, at B.L.D.E.U'S Shri. B. M. Patil Medical College Hospital and Research Center, Bijapur included 81 children between 1st Nov 2008 to Aug 2010. Total number of cases taken – 41

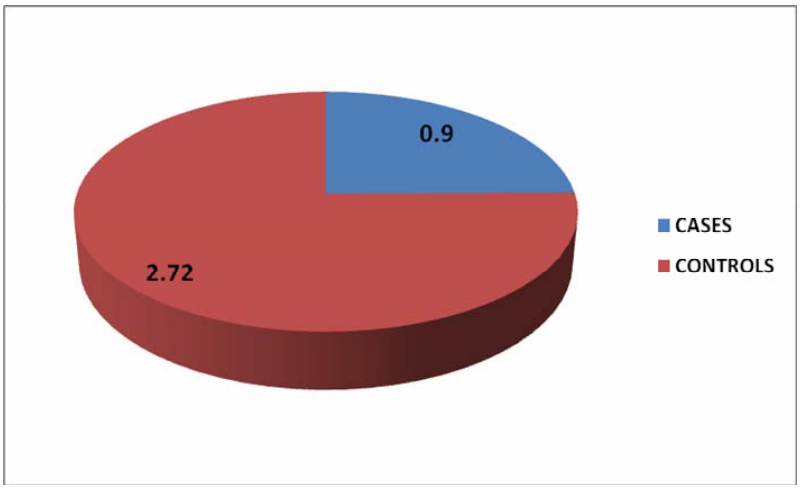
Average Serum Magnesium Levels	Cases	Controls
	0.9	2.72
Mean	0.9170	2.72
Variance	0.0324	0.452
P(T<=t) one-tail	1.2106E-20	

Total number of controls taken- 40

Average serum magnesium levels in cases and controls were.

1. Cases Vs Controls





Graph A

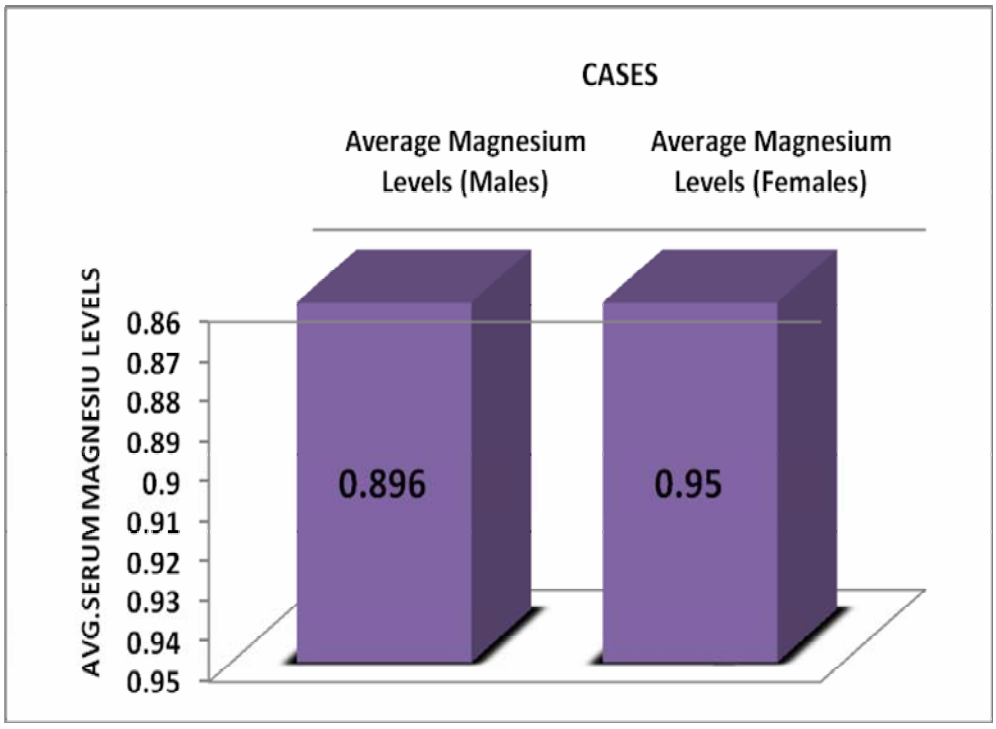
In our study Average serum magnesium levels in children with asthma was found to be 0.9, compared to 2.72 as average serum magnesium levels in controls, with a mean of 0.917 ± 0.18 in cases & in controls 2.72 ± 0.67 which was low compared to controls and was found statistically significant using t- test.(P= < 0.05)

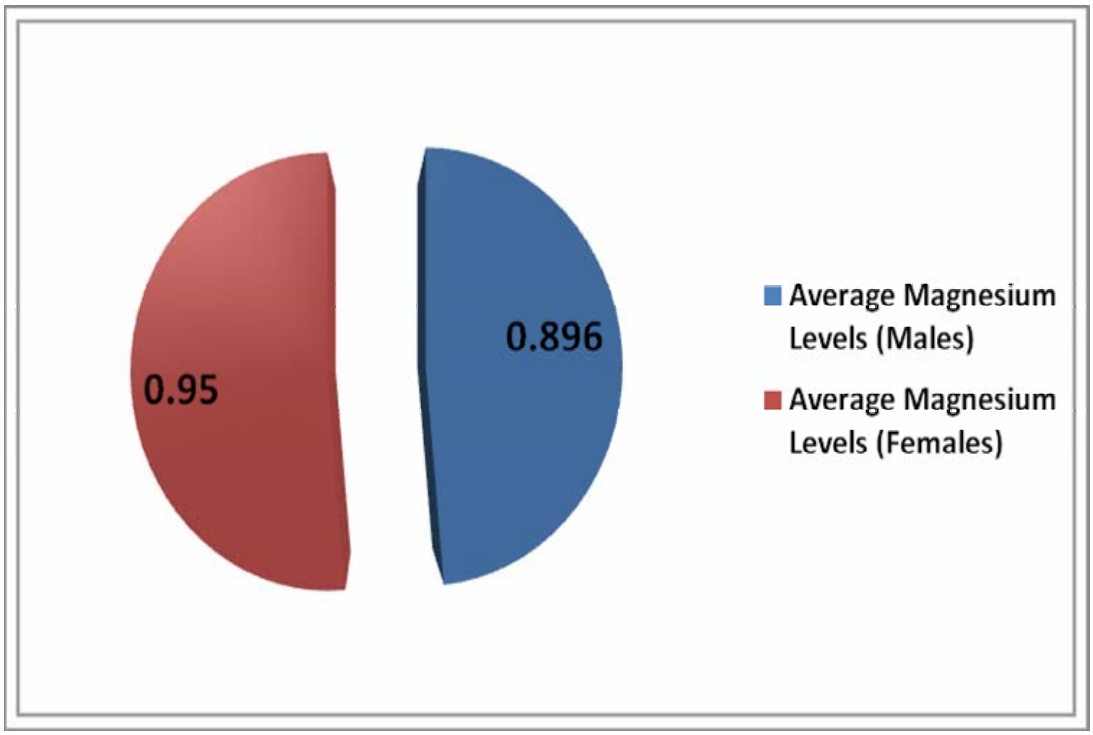
Sex Distribution

The present study was conducted in 41 asthmatic children attending pediatric opd at shri B M Patil Medical college, Bijapur. Out of a total 41 children, taken as cases with history of asthma, 16 children were females (39%) and 25 children were males (61%).

2. Cases

Average Serum Magnesium Levels	Males	Females
	0.896	0.95
Mean	0.896	0.95
Variance	0.041	0.018
P(T<=t) one-tail	0.157	





Graph B

In our study out of a total 41 children taken as cases, with 16 females (49%) and 25 males (51%), serum magnesium levels were compared between them to find out if there was any change of serum magnesium levels in males to females using t-test. The study showed that, the average change with the mean of 0.89 ± 0.64 in males & 0.95 ± 0.13 in females and it showed that there was no change in levels of serum magnesium between male and female and was statistically not significant. (P= >0.05)

Age Groups

Out of total 41 children taken as cases with history of asthma, were divided into groups

Age 3-5.11 years

Age 6-8.11years

Age 9-11.11years

Age 12-14.11 years

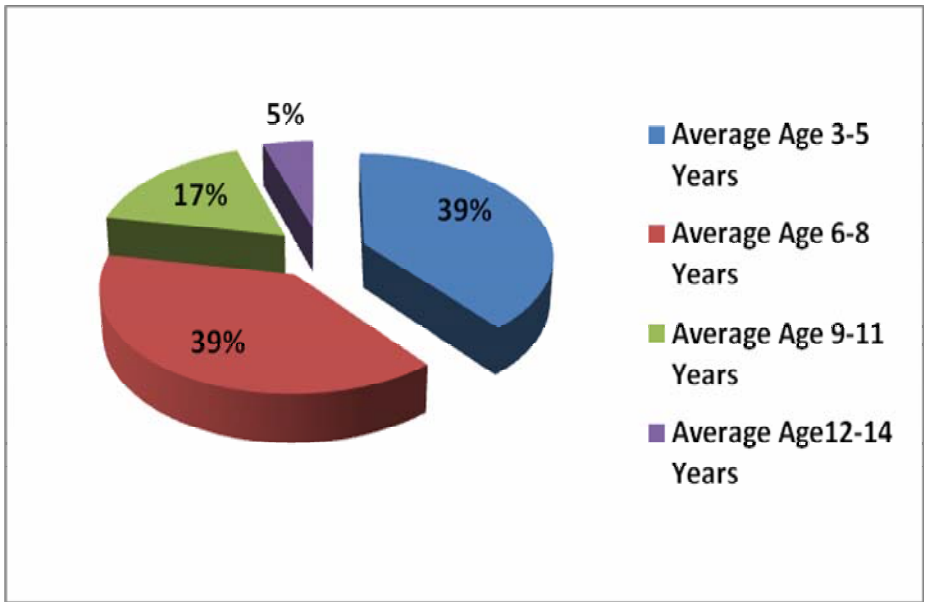
3 Age Comparison In Cases Groups

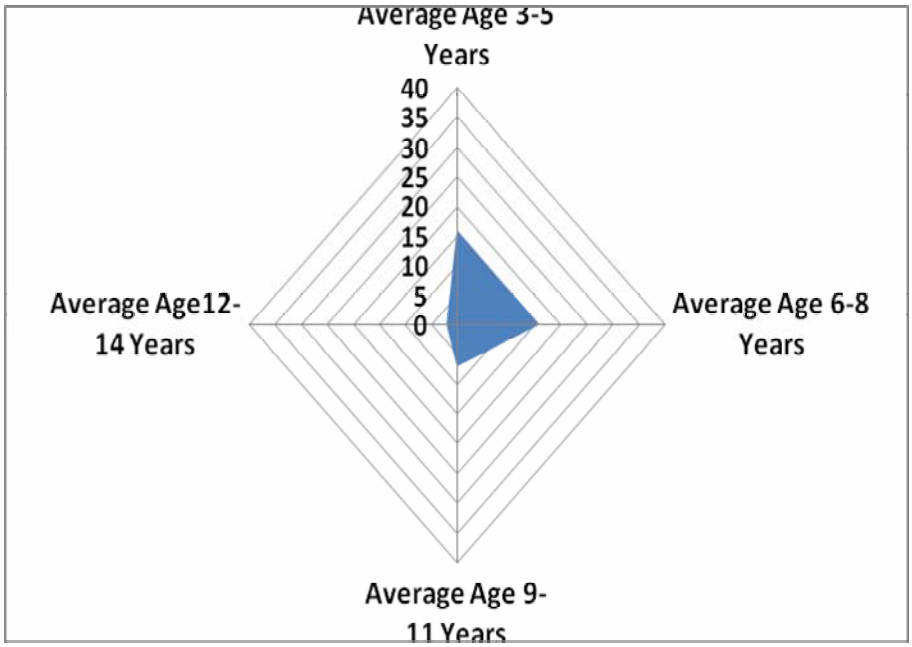
3.1 Anova: Single Factor

Sl No	Age Groups	No of Cases	Average	Variation
1	**Average Age 3-5.11 Years**	16	0.9375	0.0225
2	**Average Age 6-8.11 Years**	16	0.9188	0.0522
3	**Average Age 9-11.11 Years**	7	0.8778	0.0194
4	**Average Age12-14.11 Years**	2	0.7752	0.0102

3.2 Anova

Sl No	Source of Variation	Sum of Squares	Degree of Freedom	Mean of Squares
1	**Between Groups**	0.0206	2	0.0103
2	**Within Groups**	1.2774	38	0.0336
	Total	1.298	40	





Graph C

A comparison between age group wise distribution was done using ANOVA technique to assess the difference in the serum magnesium levels in age groups, 3 to 5.11 yrs with the mean & standard deviation of 0.93 ± 0.15 & in 6 to 8.11 yrs it was 0.91 ± 0.23, in 9 to 11.11 it was 0.87 ± 0.14, and in 12 to 14.11yrs it was 0.77 ± 0.10 and it showed that serum magnesium level variation was not significant among the age groups with p 0.737. (P= > 0.05)

GRADING OF CASES ACCORDING TO SEVERITY

The present study was conducted at department of pediatrics at Shri B M Patil Medical College, Bijapur, included 41 children in cases between age group of 3- 14 years.

They were divided into 4 grades depending on the signs and symptoms, with regard to symptoms of airflow obstruction, night time symptoms & peak expiratory flow rate.

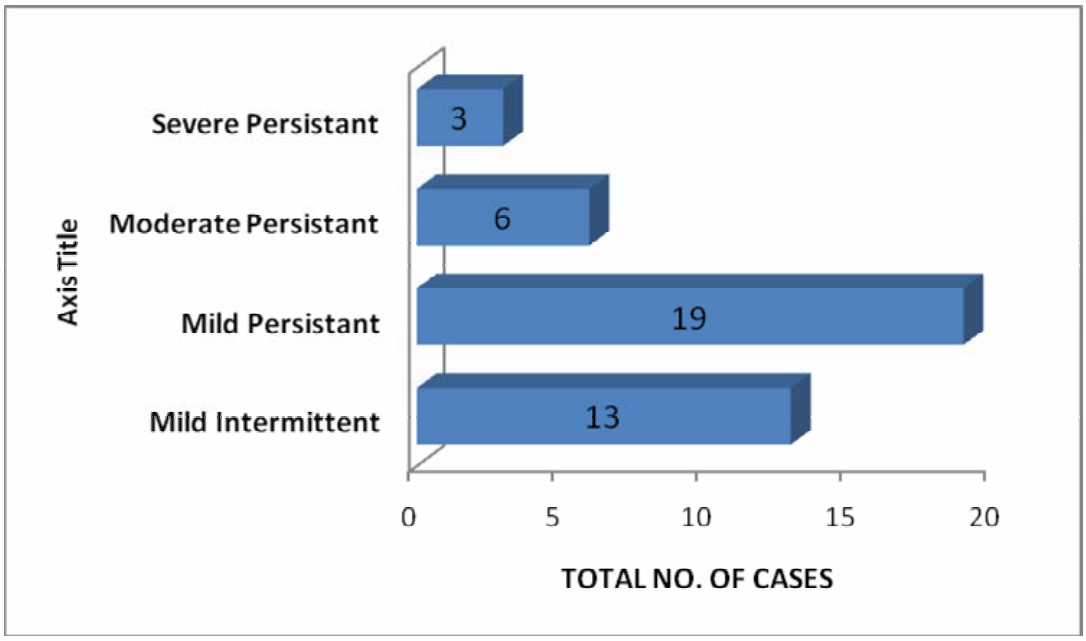
4 Grading of Asthma

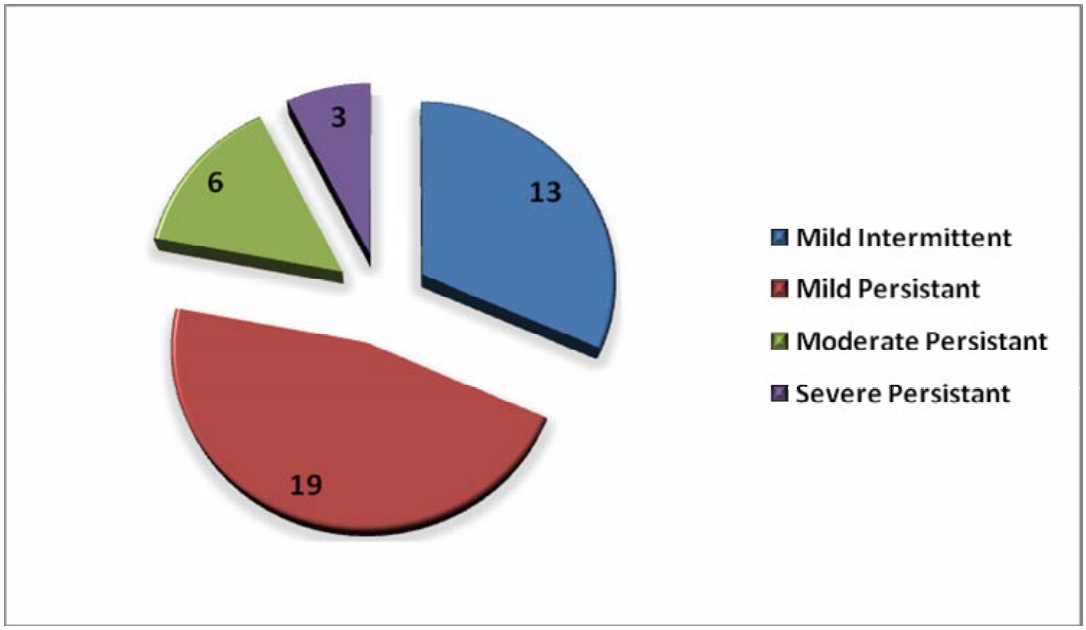
4.1 Anova : Single Factor

Sl No	Grades	No of Cases	Average	Variance
1	**Mild Intermittent**	13	1.076	0.018
2	**Mild Persistant**	19	0.915	0.010
3	**Moderate Persistant**	6	0.733	0.010
4	**Severe Persistant**	3	0.611	0.000

4.2 Anova :

Sl No	Source of Variations	Sum of Squares	Degree of Freedom	Mean of Squares
1	**Between Groups**	0.84	3	0.27879
2	**Within Groups**	0.46	37	0.01248
	Total	1.3	40	





Graph D

In our study conducted in cases, grading of cases of asthma, in grade 1 Avg. & Standard Deviation was 1.076 ± 0.14, in grade 2 it was 0.91 ± 0.10, in grade 3 it was 0.73 ± 0.10 & in grade 4 it was 0.61 ± 0.00 and it was found statistically significant with P = < 0.05. There was considerable difference between all the 4 grades at a time with P = 1. 998 E- 08.

GRADING OF CASES ACCORDING TO ACUTE EXACERBATION OF ASTHMA

The present study was conducted at department of pediatrics shri B M Patil Medical College, Bijapur, included 41 children in cases between age group of 3- 14 years.

They were divided into three grades depending on Respiratory rate, wheeze and Accessory muscle usage as

A (0-3) mild,

B (4-6) moderate

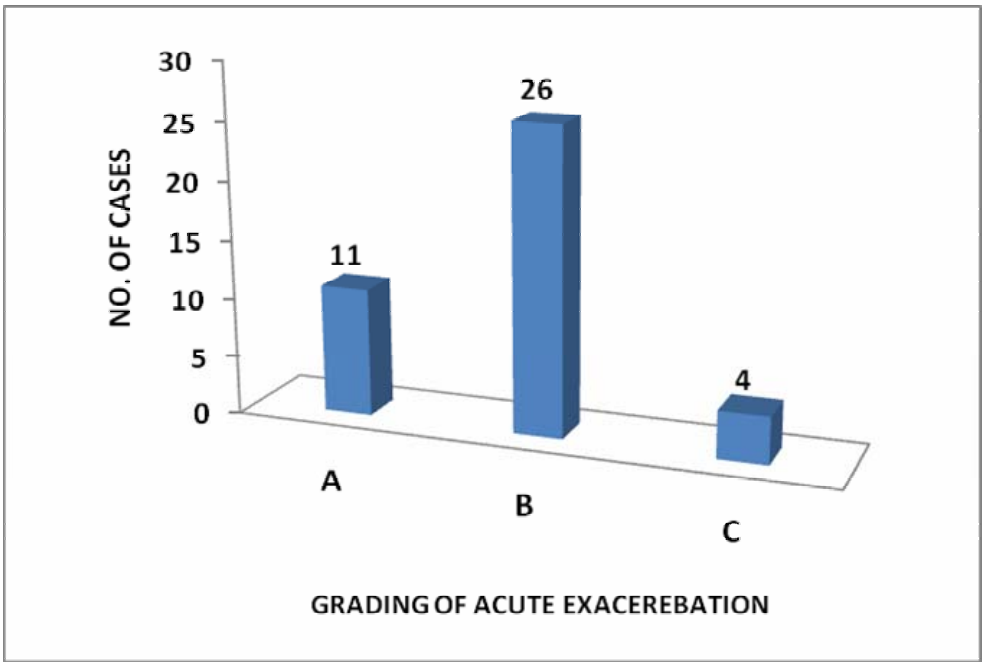
C (> 6) severe

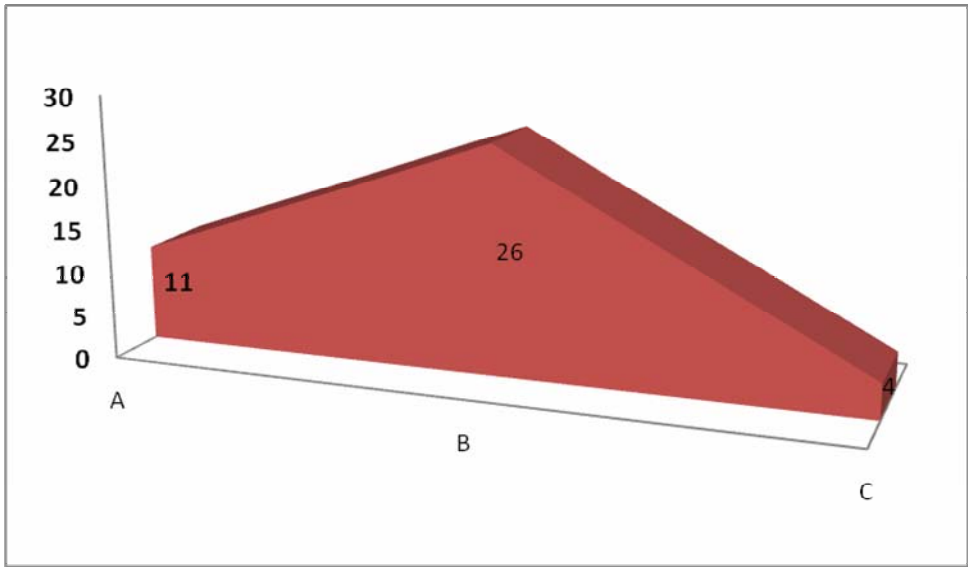
5.1 ANOVA : Single Factor

Sl No	Grading	No. of Cases	Average	Variance
1	A	11	1.454	1.8727
2	B	26	4.923	0.6338
3	C	4	6.753	2.25

5.2 ANOVA :

Sl No	Source of Variations	Sum of Squares	Degree of Freedom	Mean of Squares
1	**Between Groups**	122.481	2	61.24
2	**Within Groups**	41.32	38	1.08
	Total	163.80	40	





Graph E

A comparison with degree of severity in acute exacerbation of asthma was done in our study using ANOVA Technique using a single factor, in Group A the average and Standard Deviation was 1.454 ± 1.36, in Group B it was 4.923 ± 0.79 & in Group C it was 6.75 ± 1.5 respectively and was found to be statistically significant, with P value of 4.32 E-12. (P = < 0.05)

DISCUSSION

During this study 81 children in age group of 3-14 years were taken of which 41 children were taken as cases with history of asthma and fulfilling in the inclusion criteria and 40 children were taken as controls with no history suggestive of asthma and fulfilling exclusion criteria.

This study has shown that in asthmatic children there is significant low serum magnesium level with P= 1.2106 E-20.

In a study conducted by Mostafa sedighi et al[10], showed that there was no significant difference between plasma magnesium levels in 2 groups (P=0.06). but it also showed that intracellular magnesium levels were significantly lower (P= 0.03) in patient group.

In another study conducted by Khosrow Agin et al[11], concluded that hypomagnesemia was confirmed in chronic stable asthma in Iranian patients.

In a study conducted by Hany. S et al[92] suggested that at lower range of reference interval, serum magnesium levels are associated with increased risk of exacerbation of symptoms in asthma.

In another study conducted by Oladipo et al[93], concluded that adult Nigerian asthmatics have lower plasma magnesium concentration compared to healthy controls

SEX DISTRIBUTION

Our study included 41 children from 3- 14 years with history of asthma of which 16 children were females and 25 children were males.

A comparison between the sex was done using serum magnesium levels using t- test and was found to be of no significance in our study group, which shows that hypomagnesemia will occur equally in either of them.

In a study conducted by Khalid S et al[12], suggested that male patients had a slightly lower levels of magnesium in serum than females.

AGE GROUPS

Out of 41 cases taken as cases with history of asthma, were divided into groups of,

3-5.11years

6-8.11years

9-11.11years

12-14.11years

A comparison between groups using ANOVA Technique showed that serum magnesium levels variation was not significant among any particular age groups with P value of 0.73.

GRADING OF CASES ACCORDING TO THE SEVERITY

In our study, out of 41 children with history of asthma between the age groups 3-14 years, were divided into 4 grades depending upon the severity of signs and symptoms of airflow obstruction, night time symptoms and PEFR reading.

Our study showed that serum magnesium levels were comparatively lower in severe cases as the grades increased and was found to be statistically significant with p= 0.993 E-08.

In a study conducted by chaiwat B et al[94], concluded that serum magnesium levels in severe asthmatic patients were significantly lower than those in normal population.

GRADING OF ACUTE EXACERBATION OF ASTHMA

In our study out of 41 children in cases with history of asthma, between age group of 3- 14 years, were divided into 3 grades depending on the exacerbation of symptoms of Respiratory rate, wheeze, and Accessory muscle usage.

Our study concluded that grading of acute exacerbation of asthma was found to be statistically significant P= 4.32 E-12.

This study correlates well with Poonkasem C et al[93], and Falkner D,et al [95]which showed that hypomagnesaemia could affect the severity of exacerbations and severe attacks were leading to lower serum magnesium levels.

CONCLUSION

Average Serum magnesium levels in our study population in children attending and admitting in Pediatrics in **B.L.D.E.U'S Shri. B M Patil medical college** were significantly lower in asthmatic children than normal children. Compared to other studies our study had low serum magnesium levels in asthmatic children.

However there was no significant difference noted in serum magnesium levels in either sex and also in age groups.

Our study also concluded that with increasing severity of asthma serum magnesium levels will be significantly reduced which shows increased respiratory rate, wheeze and accessory muscle usage with the severity of asthma.

In conclusion, the serum magnesium levels in asthmatic children are lower than the normal children, and the severity and exacerbations of asthma depends on lower levels of magnesium levels.

SUMMARY

This study is carried out in the department of pediatrics, B L D E U'S Shri B M Patil Medical college, Bijapur from November 1 2008 to August 2010.

All the pediatric cases of bronchial asthma attending the out patient department and admitting to pediatric ward at hospital were taken. Healthy children aged between 3- 14 years and matching out from inclusion and exclusion criteria criteria were taken as controls.

After taking written informed consent, address and fulfilling inclusion criteria, children with bronchial asthma were included in the study. As per the proforma, detailed clinical history was recorded and children were graded depending on the symptoms and exacerebations.

3ml of venous blood is collected in a plain vial for serum magnesium estimation done by commercially available magnesium kit using the colorimetric method. Results were tabulated and compared to that of normal children taken as controls.

The statistical analysis was performed showed that, in the study group the mean serum magnesium level was 0.917 with a variance of 0.0324 and in controls mean was 2.72, with a variance of 0.452. The calculated p value was 1.2106 E- 20. i.e < 0.05 which is statistically significant.

The present study also showed that there was no significant difference in mean serum magnesium levels in either males(0.89 ± 0.64) and females (0.95 ± 0.13) in study group. The calculated p value was 0.157 and was not significant statistically.

The study group children were grouped according to the ages into 4 groups and mean serum magnesium levels compared to each group which showed that there was no significant difference among age groups with p= 0.737(statistically not significant).

The study group children were divided into 4 grades depending on the signs and symptoms with regard to symptoms of airflow obstruction, night time symptoms and PEFR. Serum magnesium levels were compared among the grades. Our study showed that with increasing severity of asthma serum magnesium levels reduced with p value of 1.998 E-08. Which was statistically significant.

The study group children were divided into 3 grades depending on respiratory rate, wheeze and accessory muscle usage. A comparison with degree of severity in acute exacerbation and was found to be statistically significant with p = 4.32 E-12.

The present study was conducted to estimate magnesium levels in asthmatic children. Also serum magnesium levels helps in indentification of asthmatic children and therby necessary precautions and prophylactic measures can be initiated.

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BLDEU'S SHRI B M PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTER BIJAPUR.

DEPARTMENT OF PEDIATRICS

TO STUDY THE CLINICAL PROFILE OF ASTHMA AND TO ESTIMATE THE SERUM MAGNESIUM LEVELS.

CASE PROFORMA

Name	**:**	**CASE NO**	**:**
Age	**:**	**IP /OP NO**	**:**
Sex	**:**	**DOA**	**:**
Religion	**:**	**DOD**	**:**
Residence	**:**		

HISTORY

Chief complaints:

History of presenting illness

History of past illness

1. History suggestive of intercurrent infections yes/no
2. History suggestive of atopy or dermatitis yes/no
3. History of hay fever /eczema yes/no
4. History of intake of any drugs yes/no

5. History of allergy to any food yes/no

6. History of any allergy to smoke/dust yes/no

7. History of exacerbation on exposure to any provoking stimuli yes/no

8. Chronic exposure to dust and smokes yes/no

9. Definite history of cough and cold yes/no

10. Recurrent attacks of rhinorrhoea and angioneuritic oedema yes/no

11. History of allergic rhinitis yes/no

12. History of recurrent wheezes yes/no

13. History of isolated coughs yes/no

14. History of recurrent breathlessness yes/no

15. History of nocturnal coughs yes/no

16. History of tightness of chest yes/no

Family history

1. History of allergy or hypersensitivity in family members yes/no
2. history of any drug allergy in family members yes/no
3. history of consanguinity yes/no
4. family size 3-5 or > or equal to 6
5. persons per room <2 or >2

Socio economic status

Housing conditions-

Indoor environment -

1. Floor pucca/kuccha
2. Walls cement/mud
3. Roof mud/cement/tar

4. Floor area	clean/dirty
5. Windows	present/absent
6. Kitchen proper ventilation	present/absent
7. Cooking gas	stove/gas cylinder/fuel burning
8. Smoke ventilation	present/absent
9. Garbage and refuse, proper disposal	yes/no

Outdoor environment

1. Site of house	closely packed/spaced
2. House nearby to factories	yes/no
3. House situated nearby to dusty areas	yes/no

Modified scale to assess socio economic conditions of the family.

(kuppuswamy scale)

Immunization history

Diet history

Medicational history

Anthropometry

1. Weight
2. Height
3. Head circumference
4. Chest circumference
5. Mid arm circumference
6. Upper segment to lower segment

General Physical Examination

1. Pallor	present/absent
2. Icterus	present/absent
3. Phlyctenular Conjunctiva	present/absent
4. Clubbing	present/absent
5. Generalized Lymphadenopathy	present/absent
6. Anasarca	present/absent
7. Built	Poor/Average /Well
8. Nourishment	Poor / Average /Well

Vitals

PR	:	BP	:
RR	:	Temp	:

Systemic Examination:

Respiratory System .

Signs

General survey

1. Decubitus-propped up at 45 degrees	yes/no
2. Cyanosis	yes/no
3. Neck veins engorged	yes/no
4. Polycythemia	yes/no
5. Purse lip respiration	yes/no

Inspection

1. Accessory muscles of respiration working yes/no

2. Wheeze yes/no

3. Indrawing of suprasternal and supraclavicular fossae yes/no

4. Shape of chest(pigeon chest) yes/no

Palpation

1. Apex beat can be localized properly yes/no

2. Trachea in midline yes/no

3. Movement of both sides of chest simultaneously yes/no
   and symmetrically

4. Vocal fremitus present yes/no

Percussion

1. Resonant note all over the chest yes/no

2. Liver dullness yes/no

Auscultation

1. Vesicular breath sounds with prolonged expiration present yes/no

2. Vocal resonance yes/no

Diagnostic criteria for asthma

More than 3 episodes of airflow obstruction with following features.

1. Recurrent wheeze yes/no

2. Recurrent isolated cough yes/no

3. Recurrent breathlessness yes/no

4. Nocturnal cough yes/no

5. Tightness of chest yes/no

6. Afebrile episodes	yes/no
7. Personal atopy	yes/no
8. Atopy/ asthma in parent/ sibling	yes/no
9. Nocturnal exacerbations	yes/no
10. Exercise / activity induced symptoms	yes/no
11. Trigger induced symptoms	yes/no
12. Seasonal exacerbations	yes/no
13. Relief with bronchodilators	yes/no

GRADING OF SEVERITY OF ASTHMA

Based on expert panel report 2[88, 89]

Grades of severity of asthma	**Symptoms of airflow obstruction**	**Night time symptoms**	**Peak expiratory flow (PEF)**
Grades 4 Severe persistant	.continuous .limited physical activity	.frequent	.less than or equal to 60% of personal best .>30% diurnal variation
Grade 3 Moderate persistant	.>once a day .attacks affect activity	>once a week	.>60% - < 80% of personal best or > 30% diurnal variation
Grade 2 Mild persistant	.>once a week but< once a day	.>twice a month	.more than or equal to 80% of personal best .20- 30 %diurnal variation
Grade 1 Mild intermittant	.<once a week .asymptomatic and normal between attacks	.<twice a month	.more than or equal to 80 % of personal best .< 20 % of diurnal variation

GRADING OF ACUTE EXACERBATION OF ASTHMA

Based on pulmonary score[90] which is a modification of the pulmonary Index[91]

Score	Respiratory rate	Wheezing present	Accessory muscle usage
	< 6 yrs > 6 yrs		
0	<30 <20	None	No apparent activity
1	31-45 21-35	Terminal expiration with stethoscope	Questionable increase
2	46-60 36-50	Entire expiration with stethescope	Increase apparently
3	>60 >50	During inspiration and expiration without stethoscope	Maximum activity
ADD Score	0-3 mild 4-6 moderate >6 severe	If wheezing absent(due to minimal air flow),score >3	

i. Cardiovascular System

ii. Central Nervous System

iii. Per abdomen examination

Provisional Diagnosis:

Investigation:

Complete Hemogram:

Hb: TC: DC:

ESR: AEC:

Blood sugar :

Chest X-ray PA view:

Serum magnesium level assay

Final Diagnosis;

CONSENT FORM

RESEARCH INFORMED CONSENT FORM

Title of Project : **"TO STUDY OF CLINICAL PROFILE OF ASTHMA IN CHILDREN AND TO ESTIMATE SERUM MAGNESIUM LEVELS IN ASTHMATICS AND ITS CORRELATION WITH ASTHMA"**

Guide : **Dr. S. V. Patil MD. (Prof & Head of the Department)**

P.G. Student : **Dr. Kiran Kumar. P.**

PURPOSE OF RESEARCH:

I have been informed that the present study will help in thorough investigation of serum magnesium levels and clinical profile of asthma.

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations a final workup for clinical and laboratory significance of the study is planned.

RISKS & DISCOMFORTS:

I understand that my child may experience some pain and discomforts during the examination or the procedure. The procedures of this study are not expected to exaggerate these feelings, which are associated with the usual course of procedure.

BENEFITS:

I understand that my participation in this study will have no direct benefit to me or my child other than the potential benefit from evaluation of serum magnesium levels in asthma and its clinical profile.

CONFIDENTIALITY:

I understand the medical information produced by this study will become part of my hospital record and will be subject to the confidentiality. Information of sensitive and personal nature will not be part of the medical record, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers, such as photographs will be used only with my special written permission. I understand that I may see the photographs before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. **Dr. Kiran Kumar. P.** at the department of Pediatrics, is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that **Dr. Kiran Kumar. P.** may terminate my participation in this study at any time after he has explained the reasons for doing so.

25. INJURY STATEMENT

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly then appropriate treatment would be available to me. But no further compensation would be provided by the hospital. I understand that by my agreement to participate in this study and not waiving any of my legal rights.

I have explained to _____ the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability.

_____ _____

Dr. Kiran Kumar. P. Date

(Investigator)

I confirm that **Dr. Kiran Kumar. P.** has explained to me the purpose of the research, the study procedure that I my child will undergo and the possible risks and discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project

_____ _____

Participant Date

_____ _____

Witness to signature Date

BIO DATA

(PG GUIDE)

NAME	**:**	**DR.S. V. PATIL**
AGE	**:**	**46 YEARS**
EDUCATIONAL QUALIFICATIONS	**:**	**MBBS (1988)** **J.N. MEDICAL COLLEGE, BELGAUM** **(KARNATAKA UNIVERSITY)** **DHARWAD** **MD (1992)** **J.N.MEDICAL COLLEGE, BELGAUM** **(KARNATAKA UNIVERSITY)** **DHARWAD**
WORK EXPERIENCE	**:**	**UG- 17 YEARS** **PG – 8 YEARS**
MEMBERSHIP	**:**	**IAP**
PRESENTLY WORKIG AS	**:**	**PROFESSOR AND HOD** **DEPARTMENT OF PEDIATRICS** **SHRI B. M. PATIL** **MEDICACOLLEGE HOSPITAL,** **BIJAPUR**

INVESTIGATOR BIO-DATA

1. NAME	**:**	**DR. KIRAN KUMAR. P**
2. QUALIFICATION	**:**	**M.B.B.S,**
		SRI DEVARAJ URS MEDICAL
		COLLEGE, KOLAR
		RAJIV GANDHI UNIVERSITY OF
		HEALTH SCIENCES, BANGALORE
		KARNATAKA.
3. K.M.C REGISTRATION NO	**:**	**70372**
4. ADDRESS FOR	**:**	**DEPARTMENT OF PEDIATRICS**
CORRESPONDANCE		**B.L.D.E.A's SHRI. B. M. PATIL**
		MEDICAL COLLEGE,
		BIJAPUR – 586103

(DR. KIRAN KUMAR. P)

KEY TO MASTER CHART

CASES

A	NAME
B	AGE
C	SEX
D	IP/ OP NUMBER
E	DATE
F	SERUM MAGNESIUM LEVELS
G	GRADING OF ASTHMA
H	STAGING OF ASTHMA

CONTROLS

A	NAME
B	AGE
C	SEX
D	IP/ OP NUMBER
E	DATE
F	SERUM MAGNESIUM LEVELS

MASTER CHARTS

CASES

Sl No	(A) Name	(B)Age	(C)Sex	(D)I.P. Number	(E) Date	(F) Serum Magnesium Levels	(G)Grading	(F)Staging of Asthma
1	**Bharath**	3yrs	M	100210	18/02/2009	0.9	2	B
2	**sahana**	3yrs	F	166777	39878	1	1	A
3	**vikas**	3yrs	M	174439	17/6/09	1.1	1	A
4	**Naveen**	3yrs	M	208247	23/12/09	1	2	B
5	**Sanjana**	4yrs	F	230533	39550	1.1	1	B
6	**Shivanand**	4yrs	M	228695	39794	0.7	3	B
7	**Devam**	4yrs	M	102561	40152	1	1	B
8	**Mallikarjuna**	4yrs	M	100402	21/5/09	0.8	2	B
9	**Sagar**	4yrs	M	4103	40240	0.9	2	B

10	**Srinivas.v**	5yrs	M		39579	0.6	4	C
11	**Akshatha**	5yrs	F	100662	27/1/09	0.9	2	B
12	**Jyothi**	5yrs	F	178917	40001	1	1	A
13	**Gopal**	5yrs	M	181226	22/7/09	1.1	2	B
14	**Revathi**	5yrs	F	2809	22/1/10	1	1	A
15	**Vaibhav**	5yrs	M	33136	27/1/10	0.8	3	B
16	**Shilpa**	5yrs	F	31061	40331	1.1	1	A
17	**Shashank**	6yrs	M	163533	40029	0.7	3	C
18	**Sachin**	6yrs	M	162450	23/4/09	0.9	2	B
19	**krishna**	6yrs	M	192501	20/8/09	1.5	1	A
20	**Gopi**	6yrs	M	192991	39822	1	2	B
21	**Prakash**	6yrs	M	203431	39856	1.1	2	B
22	**Afsana**	7yrs	F	235148	30/12/08	0.6	4	C
23	**Rahul**	7yrs	M	168674	17/4/09	1.1	1	A

24	**Kartik**	7yrs	M	210297	39880	0.6	3	B
25	**Nauranjan**	7yrs	M	192847	39822	1	1	A
26	**Rohan**	7yrs	M	193517	15/9/09	0.7	3	B
27	**Ashish**	7yrs	M	5782	40360	0.8	2	B
28	**Pooja**	8yrs	F	218572	13/11/08	1	1	A
29	**Sanjeev**	8yrs	M	10772	40123	0.9	2	B
30	**shrusti.b**	8yrs	F	38315	24/2/09	1.1	1	A
31	**Kshama**	8yrs	F	11177	16/8/09	0.8	2	B
32	**Kavya**	8yrs	F	263280	40269	0.9	2	B
33	**Lakshmi**	10yrs	F	9042	24/3/09	0.9	2	B
34	**Sanjeev**	10yrs	M	93512	30/4/09	0.6	4	C
35	**Sonu**	10yrs	F	187627	20/8/09	0.9	2	B
36	**Bhavana**	10yrs	F	201093	39881	1.1	2	B
37	**Promod**	10yrs	M	4195	40271	0.9	2	B

38	**Deepthi**	11yrs	F	163511	39848	1	1	A
39	**Siddanagouda**	11yrs	M	4004	40240	0.9	3	B
40	**Vinayak**	12yrs	M	215223	39489	0.8	2	B
41	**Nirmala**	12yrs	F	4055	40240	0.8	2	B

CONTROLS

Sl No	(A) Name	(B) Age	(C) Sex	(D) I. P. Number	(E) Date	(F) Serum Magnesium Levels
1	**Akhilesh**	4yrs	M	13582	24/6/10	2.6
2	**Savithri**	4yrs	F	13773	26/6/10	3.2
3	**Manjunath**	4yrs	M	13241	28/6/10	3.6
4	**Sneha**	4yrs	F	14167	30/6/10	2.5
5	**Anand**	4yrs	M	14056	28/6/10	3.8
6	**Nagesh**	5yrs	M	13795	26/6/10	2.1
7	**Sunil**	5yrs	M	13754	26/6/10	1.9
8	**Renuka**	5yrs	F	13938	28/6/10	2.6
9	**Sunil**	5yrs	M	13734	28/6/10	3.2
10	**Raju**	5yrs	M	13164	28/6/10	3.3
11	**Sanjay**	5yrs	M	14217	30/6/10	2.9

12	**Akash**	6yrs	M	13706	24/6/10	3.1
13	**Ujwala**	6yrs	F	13904	26/6/10	1.9
14	**Vasudev**	6yrs	M	13748	26/6/10	1.7
15	**Akshay**	6yrs	M	14033	28/6/10	3.1
16	**Divya**	6yrs	F	14174	30/6/10	1.8
17	**Pallavi**	6yrs	F	14270	30/6/10	3.2
18	**Akash**	6yrs	M	15426	30/6/10	2.5
19	**sangeetha**	7yrs	F	13766	24/6/10	2.1
20	**Renawwa**	7yrs	F	13483	24/6/10	3.3
21	**Vaishnavi**	7yrs	F	13746	28/6/10	2.9
22	**Rahul**	7yrs	M	14266	30/6/10	3.8
23	**Pooja**	8yrs	F	13804	24/6/10	2.8
24	**Sampath kumar**	8yrs	M	13750	26/6/10	1.9

25	**Durgavva**	9yrs	F	13855	26/6/10	3.7
26	**Akhilesh**	9yrs	M	13580	24/6/10	1.7
27	**Prakash**	9yrs	M	12103	28/6/10	1.6
28	**Kavitha**	9yrs	F	12107	28/6/10	2.6
29	**Prakash**	10yrs	M	13708	24/6/10	3.1
30	**Srishail**	10yrs	M	13731	24/6/10	1.9
31	**Aarthi**	10yrs	F	13940	28/6/10	1.7
32	**Rakesh**	10yrs	M	12105	28/6/10	3.3
33	**Chidanand**	10yrs	M	14213	30/6/10	3.6
34	**Seeru**	12yrs	M	13524	26/6/10	2.6
35	**Shilpa**	12yrs	F	14207	30/6/10	2.9
36	**Rajesh**	12yrs	M	13521	26/6/10	3.2
37	**Sanvi**	13yrs	F	13478	24/6/10	2.5
38	**Abhishek**	13yrs	M	12116	28/6/10	3.3

39	**Naveen**	14yrs	M	14139	30/6/10	1.9
40	**vivek**	14yrs	M	13986	30/6/10	3.4