ASSESSMENT OF LUNG FUNCTIONS IN PATIENTS TREATED FOR H1N1 INFLUENZA

Dissertation submitted in partial fulfillment of

requirement for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH 1

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DECLARATION

I solemnly declare that this dissertation entitled "ASSESSMENT OF LUNG FUNCTIONS IN PATIENTS TREATED FOR H1N1 INFLUENZA" was done by me at Madras Medical College and Government General Hospital, Chennai , during 2008 – 2011 under the guidance and supervision of Prof. P.CHITRAMBALAM, M.D. This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-1)

Place : Chennai-03 Signature of the Candidate

Date :

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CERTIFICATE

This is to certify that the dissertation entitled "**ASSESSMENT OF LUNG FUNCTIONS IN PATIENTS TREATED FOR H1N1 INFLUENZA**" is a bonafide work done by **Dr.P.NAVEENKUMAR,** at Madras Medical College and Government General Hospital, Chennai-03 in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-1) under my guidance and supervision during the academic year 2008-2011.

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CONTENTS

INTRODUCTION

INTRODUCTION

Acute viral infections of the respiratory tract especially the lower respiratory tract are well known cause of airway diseases in later life. They have effects on bothin normal and in diseased airways.

Almost all known viral respiratory infections tends to produce deletrious effects on the pulmonary functions especially obstructive type of airway diseases due to airway hyper responsiveness.

Certain viruses seem to have a particular propensity to cause wheezing, RSV being most common, followed by the parainfiuenza viruses and coronaviruses. Other viruses like influenza and rhinovirus also produce the same effects in normal lung and also they are responsible for the acute exacerbations of wheeze in patients with airway diseases like bronchial asthma and chronic obstructive airway disease.

Even "uncomplicated" viral respiratory infection in adults, ***ie,*** infections with clinical manifestations limited to the upper respiratory tract, and normal chest roentgenograms, is commonly associated with prolonged physiologic abnormalities, suggestive of lower respiratory tract involvement.

H1N1 flu infection produced a significant morbidity and mortality during the acute stage of infection during the year 2009 and continued to 2010. Being a viral respiratory infection it can also produce some detrimental effect on pulmonary function as like its fellow viruses.

OBJECTIVES OF THE STUDY

1. To assess the clinical status of the patients who were previously treated for H1N1 influenza.

2. To determine the pulmonary function of those patients by spirometry.

3. To determine the relationship between the severity of the lung involvement during the acute infection and the extent of residual effect on the lung fuction.

REVIEW OF LITERATURE

Viral respiratory tract infections may well be the most common ofall mankind's illnesses. It includes both upper and lower respiratory tract infections. Defined etiologic agents include rhinovirus, coronavirus, and parainfluenza virus, but in approximately 75 percent of the cases, no etiologic agent can be identified[1]. In addition to the classic signs of coryza and pharyngitis, these illnesses are often associated with cough and decreased exercise tolerance more suggestive of lower respiratory tract involvement. A number of physiologic studies have demonstrated alterations in pulmonary function.

Picken et al [2] documented abnormal frequency dependent dynamic compliance suggestive of peripheral airway abnormalities following hinovirus infections. In some instances, these abnormalities developed four to eight weeks after the acute onset of illness and did not return to normal for an additional six weeks .Cate et al[3] demonstrated diminished steady state diffusing capacity measurements in subjects with rhinovirus infection, felt to be caused by transient bronchiolitis.

Fridy and coworkers[4] found abnormal closing volumes and diminished density dependent expiratory flow rates in smokers with predominantly rhinovirus disease studied prospectively. In a recent prospective study of young children 2.5 to 11 years of age, uncomplicated upper respiratory tract infections were uniformly associated with diminished forced expiratory flow rates.[5] This study is of particular importance since other complicating risk factors such as smoking and long-term air pollution exposure would be obviated.

More recent attention has focused on the pathophysiology of influenza virus infections. It has long been appreciated that individuals with underlyingchronic obstructive pulmonary disease are susceptible to serious, life-threateningpulmonary complications of influenza infection.[6] Moreover, these casesrepresent only a small minority of the estimated 20 percent to 50 percent of the population at risk who are infected during a pandemic. Previous studies have suggested that pulmonary function abnormalities frequently follow influenza infection, even in the absence of pneumonia.[7] Forseveral sequential years, we have studied airway mechanics in groups ofotherwise healthy young adults with nonpneumonic naturally acquired influenzaA (H3N2) infection.

The findings in these studies suggests the presence of uneven airway time constants, and we theorized that a generalized increase in flow resistance in peripheral airspaces could result in the degree of frequency dependence of resistance. As was noted with other viral infections, these mechanical abnormalities persisted beyond the period of symptomatic illness.

PATHOPHYSIOLOGY OF VIRUS-LUNG INTERACTION

Bronchial Inflammation and Airway Hyper responsiveness

The interactions between virus and host are very complicated.

Although the relationship between respiratory viral infections and the onset of asthma has not been entirely defined, a link between exacerbations of bronchial inflammation and enhancement of allergic airway responses is much more clear. Acute infection can intensify airway narrowing and airway hyperresponsiveness (AHR). Viral-induced alterations of epithelial cell structure and function, increased inflammatory cell accumulation in the tissue and around airways , edema of airway walls, and exposure of airway nerve endings in sites of epithelial cell sloughing contribute to altered airway function.[8] These alterations in airway function may contribute to asthma exacerbation.

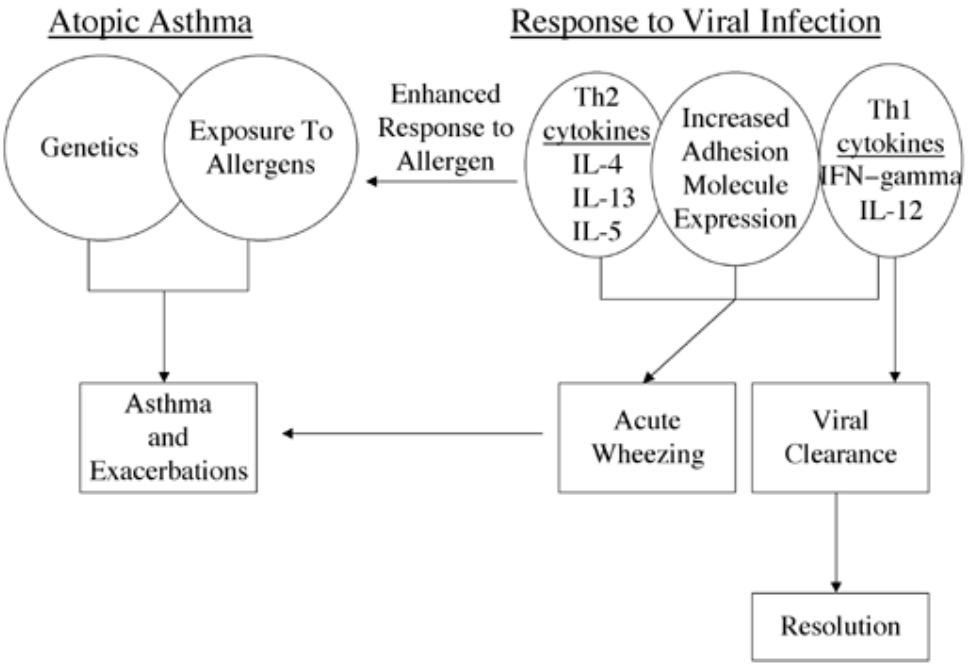
Viral-Induced Effectors of the Inflammatory Response

Adhesion Molecules

The complexity of the effects of respiratory infection on airway function are underscored by the many cell-mediated immune responses to viruses (Figure). Increased expression of a number of important adhesion molecules can be detected in response to infection. These proteins regulate inflammatory cell migration, enhancing airway

inflammatory responses. One example is intercellular adhesion molecule 1 (ICAM-1), a molecule in which expression is increased during and following viral infection. ICAM-1 is expressed on a wide variety of cells, including epithelial cells, endothelial cells, fibroblasts, lymphocytes, and monocytes. Expression of ICAM-1 is increased by the pro-inflammatory mediators (cytokines) interferon-gamma, interleukin (IL)-1, and tumor necrosis factor (TNF).

ICAM-1 is the major human rhinovirus receptor. Upregulation of ICAM-1 has been detected following experimental rhinovirus infection. Binding of the virus to ICAM-1 on different cell types triggers the release of a number of cytokines and further increases in ICAM-1 expression on adjacent cells, thereby enhancing adhesion and spread of the virus. With increased expression of ICAM-1, eosinophil and neutrophil migration, adhesion and attraction are augmented; this leads to enhanced inflammation, which increases AHR. Support for this pathway in the pathogenesis of disease is provided by studies in different animal models where blockade of ICAM-1 reduces inflammatory cell accumulation.



Chemokines and Cytokines

Many of the respiratory viruses, but especially RSV, can affect the respiratory epithelium, triggering the release of both eosinophil chemoattractants (eg, Rantes) and IL-6, IL-8, GM-CSF, and macrophage inflammatory protein (MIP-1alpha) . In a recent study of RSV-stimulated neutrophils, the release of IL-8 and MIP-1 beta and neutrophil degranulation were demonstrated.[9] Rantes is a potent chemoattractant for eosinophils, while GM-CSF is important for eosinophilopoiesis. IL-8 will lead to the influx of neutrophils, which, in turn, can further contribute to

inflammation by the release of their stored/de novo synthesized chemokines and granular enzymes.

MIP-1 alpha stimulates eosinophil and basophil chemotaxis and degranulation, which leads to further recruitment of these cells and the subsequent release of eosinophil cationic proteins (ECP) and histamine into the airways.

MIP-1 beta is a member of the c-c chemokine family. Its function is not fully defined, but it appears capable of stimulating antigen-specific Th2 lymphocyte proliferation and upregulating the costimulatory molecule CD80 on antigen-presenting cells. Of note, ECP, eosinophil neurotoxin, and histamine have been identified in the respiratory secretions of bronchoalveolar lavage fluid of infants with RSV bronchiolitis. Neutrophils, IL-8, and neutrophil myeloperoxidase have also been found in the respiratory secretions of children with viral-induced asthma.

Another inflammatory mechanism possibly involved in the development of asthmatic symptoms may be the increase in production of IL-11 by epithelial cells following viral infection. In children with viral upper RTI and in those with wheezing, IL-11 levels are elevated in nasal secretions. Administration of recombinant IL-11 into the lungs of mice results in increased airway responsiveness to methacholine. The role IL-11 plays in virus-induced lung disease remains to be determined.

Eosinophils and M2 Receptor Dysfunction

The inflammatory response elicited by viral RTI and particularly the accumulation of eosinophils most likely play essential roles in the development of wheezing during acute infection. The study authors have recently reported in a murine model[10,11] that the eosinophilic component of the inflammatory response to acute RSV infection and the associated development of AHR to methacholine provocation are dependent on the presence of IL-5. Blockade of the eosinophil adhesion molecule VLA-4 prevented both eosinophil migration into the airways and the associated development of AHR. These data extend some of the clinical observations that development of RSV – induced AHR is associated with the presence of eosinophils and may be dependent on this eosinophilic response.

Dependence of virus-induced AHR on IL-5 has also been reported in a guinea pig model of influenza infection. Studies in guinea pigs revealed a mechanism by which eosinophils could influence airway tone and reactivity. Cationic proteins released by eosinophils are capable of binding to presynaptic M2 muscarinic receptors on postganglionic parasympathic airway nerves. The resulting blockade interrupts an inhibitory feedback mechanism, resulting in increased release of acetylcholine and in increased airway muscle tone and reactivity. This mechanism has been demonstrated both in models of allergic sensitization

and following acute viral infection. Parainfluenza neuraminidase can also bind to M2 muscarinic receptors directly and may be responsible for effects described in the absence of eosinophilic inflammation. In addition, viral infection and interferon-gamma downregulate M2 receptor gene expression.

Noninflammatory Mechanisms in Virus-Induced Wheezing

Additional noninflammatory mechanisms may contribute to the development of wheezing following viral RTI. Viral infection of respiratory epithelium results in reduced nitric oxide production associated with AHR in guinea pigs. Nitric oxide is the putative bronchodilator agonist of the non - adrenergic, noncholinergic inhibitory (NANCi) system. This system can be defective during and after respiratory viral infection resulting in AHR, as demonstrated in a study of RSV infection of cotton rats.[12]

A reduced barrier function of the respiratory epithelium may expose sensory C fibers to enhanced stimulation. This results in the release of neuropeptides, such as substance P and neurokinin A, both agonists of the nonadrenergic, noncholinergic activating system; further, it induces a brainstem reflex leading to bronchoconstriction. Neuropeptides can also contribute to airway obstruction by causing increased leukotriene synthesis, release of mast cell mediators, and increased mucus secretion.

In addition, infected epithelial cells produce smaller amounts of neutral endopeptidase, an enzyme that degrades neuropeptides. The role of sensory C fibers in virus - induced asthma exacerbations in humans remains controversial. Bradykinin provocation following experimental rhinovirus infection in mild asthmatics does not result in increased bronchial hyperresponsiveness. Bradykinin is a strong stimulator of sensory C fibers and may be expected to cause increased bronchial hyperresponsiveness if this system plays a major part in virus - induced asthma.

Persistence of Infection

At present, the mechanisms by which acute respiratory tract virus infection can affect the development of asthma long after the infection has resolved are unclear. Some of the pathologic changes may simply persist for long periods after the acute infection. A defect in NANCi function has been demonstrated to last for up to 24 weeks following RSV infection in ferrets. Persistence of infection, resulting in chronic alterations of epithelial cell function and chronic inflammation, is supported by findings in guinea pigs and calves where RSV antigen can be detected in the lung 6 and 12 weeks after the infection. In guinea pigs, this persistence is associated with persistent AHR.

Interactions Between Viral RTI and Allergic Sensitization

To define potential mechanisms of interaction between viral RTI and allergic sensitization to inhaled allergens, a number of rodent models have been developed. The majority of these models showed increased allergic sensitization following respiratory virus infection, resulting in eosinophilic airway inflammation and AHR. In some of these models, animals were first exposed to allergen during the acute infection phase followed by subsequent allergen challenges, resulting in increased allergic sensitization with elevated serum levels of allergen – specific IgE.

In these experimental approaches, enhanced allergic sensitization was potentially due to increased allergen uptake across inflamed mucous membranes. Indeed, in both a guinea pig and a mouse model, exposure to ovalbumin aerosol caused increased levels of serum ovalbumin if administered during acute virus infection.

Schwarze and colleagues[10] reported on a murine model of RSV infection and subsequent sensitization to aerosolized ovalbumin. In this model, exposure to allergen over 10 days was begun only after the resolution of the acute (RSV) infection. This resulted in enhanced responses to allergen and, as a consequence, airway inflammation with the influx of neutrophils and eosinophils. This was associated with altered airway responsiveness to inhaled methacholine.

In contrast to many of the models discussed above, allergen – specific IgE serum levels were not higher in the group that was infected with RSV prior to allergic sensitization. This may indicate that mechanisms other than increased allergen uptake are likely responsible for the effects of RSV infection on the subsequent exposure to allergen. As demonstrated, sensitization following acute RSV infection triggers eosinophilic inflammation and associated AHR. Anti-IL-5 treatment during the allergen exposure phase prevents lung eosinophilia and the development of AHR.

Influenza and lung function

More recent attention has focused on the pathophysiology of influenza virus infections. It has long been appreciated that individuals with underlying chronic obstructive pulmonary disease are susceptible to serious, life-threatening pulmonary complications of influenza infection.[13] Moreover, these cases represent only a small minority of the estimated 20 percent to 50 percent of the population at risk who are infected during a pandemic.

Previous studies have suggested that pulmonary function abnormalities frequently follow influenza infection, even in the absence of pneumonia.[14] For several sequential years, they have studied airway

mechanics in groups of otherwise healthy young adults with nonpneumonic naturally acquired influenza A (H3N2) infection.

During the initial three weeks following onset of symptoms, subjects demonstrated frequency dependence of total pulmonary resistance.[15] This finding suggests the presence of uneven airway time constants, and they theorized that a generalized increase in flow resistance in peripheral airspaces could result in this degree of frequency dependence of resistance.[16] As was noted with other viral infections, these mechanical abnormalities persisted beyond the period of symptomatic illness.

In a subsequent epidemic, they were able to further evaluate peripheral airway mechanics in uncomplicated influenza infection by demonstrating diminished density – dependent forced flow rates in volunteers with naturally acquired illness[17] Again, these abnormalities persisted for some three to five weeks following onset. Furthermore, when atopic subjects were compared to normals, no difference in density – dependent flow rates was observed, suggesting that these abnormalities were not related to pre-existing abnormal airway sensitivity.

As compared to the other viruses influenza virus induced pulmonary function alterations tends to persist for longer period even upto one year.

Currently, there is much interest in the development of live vaccines against respiratory viruses, especially influenza.[45] Since prolonged peripheral airway dysfunction is a common sequelae to naturally acquired infection, evaluation of various candidate vaccines logically should include some physiologic testing. Several such studies have been done, and although results are somewhat variable, there is, at present, no evidence that live influenza virus vaccines have serious deleterious effect on lung funclion.[46] [47] [51]

VIRAL INFECTIONS AND DISEASED LUNG

Historically, bacteria have been considered the main infectious cause of COPD exacerbations.[18] A growing body of evidence, however, implicates viral upper respiratory tract infections (URIs) as the predominant risk factor associated with exacerbations of COPD.[19] Approximately 40-60% of all COPD exacerbations are associated with URIs. [20,21,22] This figure may actually underestimate the true impact that viruses have on individuals with COPD. For instance, it is well recognized clinically that upper respiratory tract cold symptoms often precede COPD exacerbations by days to weeks. Therefore, clinical studies that sample for viruses during a COPD exacerbation fail to detect virus despite using highly sensitive PCR technology.

The major respiratory viruses associated with exacerbations of COPD are as follows:[48]

1. rhinovirus;
2. coronavirus;
3. influenza;
4. parainfluenza;
5. adenovirus;
6. respiratory syncytial virus (RSV).

The prevalence of each of these viruses can vary widely depending on geography and local epidemiologic trends. For example, a recent Hong Kong study [23] found that influenza was the most common virus identified in patients hospitalized with COPD exacerbations[49] [50]. The high prevalence of influenza in that study, however, may have been due to the relatively low influenza vaccination rate (40.3%) among study participants. By contrast , the relatively low prevalence of influenza seen in a prospective cohort from a London outpatient clinic [24] was most likely attributable to the 74% influenza vaccination rate among that population.

SWINE FLU

Influenza A (H1N1) virus is a subtype of influenza A virus and was the most common cause of human influenza (flu) in 2009. Some strains of H1N1 are endemic in humans and cause a small fraction of all influenza-like illness and a small fraction of all seasonal influenza. H1N1 strains caused a few percent of all human flu infections in 2004–2005.[25]

Swine influenza (also called swine flu, hog flu, or pig flu) is an infection by any one of several types of swine influenza virus. Swine influenza virus (SIV) is any strain of the influenza family of viruses that is endemic in pigs. As of 2009, the known SIV strains include influenza C and the subtypes of influenza A known as H1N1, H1N2, H3N1, H3N2, and H2N3.[49]

Swine influenza virus is common throughout pig populations worldwide. Transmission of the virus from pigs to humans is not common and does not always lead to human influenza, often resulting only in the production of antibodies in the blood. If transmission does cause human influenza, it is called zoonotic swine flu. People with regular exposure to pigs are at increased risk of swine flu infection.

Pigs experimentally infected with the strain of swine flu that is causing the current human pandemic showed clinical signs of flu within four days, and the virus spread to other uninfected pigs housed with the infected ones.[26]

BACKGROUND

The epidemiology of pandemic (H1N1) 2009 virus infection to date indicates that children and young adults have had the highest attack rates. A wide clinical spectrum of disease ranging from non-febrile, mild upper respiratory tract illness, febrile influenza like illness (ILI) to severe or even fatal complications, including rapidly progressive pneumonia has been described. The most commonly reported symptoms have included cough, fever, sore throat, muscle aches, malaise, and headache. Some patients have experienced gastrointestinal symptoms (nausea, vomiting, and/or diarrhoea).

Approximately 10-30% of hospitalized patients in some countries have required admission to intensive care units (ICU). Critically ill patients include those who experienced rapidly progressive lower respiratory tract disease, respiratory failure, and acute respiratory distress syndrome (ARDS) with refractory hypoxemia. Other severe complications have included secondary invasive bacterial infection, septic shock, renal

failure, multiple organ dysfunction, myocarditis, encephalitis, and worsening of underlying chronic disease conditions such as asthma, chronic obstructive pulmonary disease (COPD), or congestive cardiac failure.

RISK FACTORS FOR SEVERE DISEASE

From pandemic (H1N1) 2009 virus infection reported to date are considered similar to those risk factors identified for complications from seasonal influenza.

These include the following groups:

- Infants and young children, in particular <2 years
- Pregnant women
- Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
- Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure)
- Persons with metabolic disorders (e.g. diabetes)
- Persons with chronic renal disease, chronic hepatic disease, certain neurological conditions (including neuromuscular, neurocognitive, and seizure disorders),

• Hemoglobinopathies, or immunosuppression, whether due to primary Immunosuppressive conditions, such as HIV infection, or secondary conditions, such as immunosuppressive medication or malignancy,

• Children receiving chronic aspirin therapy

• Persons aged 65 years and older.

A higher risk of severe complications from pandemic (H1N1) 2009 virus infection has also been reported in individuals who are obese (particularly in those who are morbidly obese) and among disadvantaged and indigenous populations.

On average, about 1/2 of hospitalized patients have had at least one or more underlying medical conditions. However, about 1/3 of patients with very severe illness admitted to ICU were previously healthy persons.

The incubation period appears to be approximately 2-3 days , but could range up to 7 days.

CASE DESCRIPTION

Uncomplicated influenza

• ILI symptoms include: fever, cough, sore throat, rhinorrhea, headache, muscle pain, and malaise, but no shortness of breath and no dyspnoea. Patients may present with some or all of these symptoms.

Gastrointestinal illness may also be present, such as diarrhoea and/or vomiting, especially in children, but without evidence of dehydration.

Complicated or severe influenza

• Presenting clinical (e.g. shortness of breath / dyspnoea, tachypnea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia), central nervous system (CNS) involvement (e.g . encephalopathy, encephalitis), severe dehydration, or presenting secondary complications, such as renal failure, multiorgan failure, and septic shock. Other complications can include rhabdomyolysis and myocarditis.

• Exacerbation of underlying chronic disease, including asthma, COPD, chronic hepatic or renal failure, diabetes, or other cardiovascular conditions.

• Any other condition or clinical presentation requiring hospital admission for clinical management.

• Any of the signs of disease progression listed below.

Signs and symptoms of progressive disease

Patients who present initially with uncomplicated influenza may progress to more severe disease. Progression can be rapid (i.e. within 24 hours). The following are some of the indicators of progression, which would necessitate an urgent review of patient management:

• Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency:

- Shortness of breath (with activity or at rest), difficulty in breathing, turning blue, bloody or coloured sputum, chest pain, and low blood pressure;

- In children, fast or laboured breathing; and

- Hypoxia, as indicated by pulse oximetry.

• Symptoms and signs suggesting CNS complications:

- Altered mental status, unconsciousness, drowsiness, or difficult to awaken and recurring or persistent convulsions (seizures), confusion, severe weakness, or paralysis.

• Evidence of sustained virus replication or invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond 3 days).

• Severe dehydration, manifested as decreased activity, dizziness, decreased urine output, and lethargy.

PREGNANCY AND H1N1 INFLUENZA

Pregnant women, especially those with co-morbidities, are at increased risk for complications from influenza virus infection. Influenza in pregnancy is associated with an increased risk of adverse pregnancy outcomes, such as spontaneous abortion, preterm birth, and fetal distress. Consequently, pregnant women with suspected or confirmed pandemic (H1N1) 2009 virus infection warrant closer observation and early antiviral treatment (see below section on antivirals). Paracetamol (acetaminophen) is recommended to ease fever and pain in pregnant women, as non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, are associated with fetal risks and maternal bleeding and are, therefore, contraindicated in pregnancy.

GUIDELINES ON CATEGORIZATION OF INFLUENZA A H1N1 CASES DURING SCREENING FOR HOME ISOLATION, TESTING TREATMENT, AND HOSPITALIZATION[27]

In order to prevent and contain outbreak of Influenza-A H1N1 virus for screening, testing and isolation following guidelines are to be followed:

At first all individuals seeking consultations for flu like symptoms

should be screened at healthcare facilities both Government and private or examined by a doctor and these will be categorized as under:

Category- A

Patients **with mild fever plus cough / sore throat** with or without

body ache, headache, diarrhoea and vomiting will be categorized as Category-A. They **do not require** Oseltamivir and should be treated for the symptoms mentioned above. The patients should be monitored for their progress and reassessed at 24 to 48 hours by the doctor.

No testing of the patient for H1N1 is required.

Patients should confine themselves at home and avoid mixing up with public and high risk members in the family**.**

Category-B

(i) In addition to all the signs and symptoms mentioned under Category-A, if the patient has high grade fever and severe sore throat, may require home isolation and Oseltamivir;

(ii) In addition to all the signs and symptoms mentioned under Category-A, individuals having one or more of the following high risk conditions shall be treated with Oseltamivir:

Children with mild illness but with predisposing risk factors.

Pregnant women;

Persons aged 65 years or older;

Patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS;

Patients on long term cortisone therapy.

No tests for H1N1 is required for Category-B (i) and (ii).

All patients of Category-B (i) and (ii) should confine themselves at home and avoid mixing with public and high risk members in the family.

Category-C

In addition to the above signs and symptoms of Category-A and B, if the patient has one or more of the following:

Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discolouration of nails;

Children with influenza like illness who had a severe disease as manifested by the red flag signs (Somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc).

Worsening of underlying chronic conditions.

All these patients mentioned above in Category-C require testing, immediate

hospitalization and treatment.

H1N1 INFLUENZA A GLOBAL BURDEN

The **2009 flu pandemic** was a global outbreak of a new strain of H1N1 influenza virus, often referred to as "**swine flu**". [28] First described in April 2009 , the virus appeared to be a new strain of H1N1 which resulted when a previous triple reassortment of bird, pig, and human flu viruses further combined with a Eurasian pig flu virus.[29]
The outbreak began in the state of Veracruz, Mexico, with evidence that there had been an ongoing epidemic for months before it was officially recognized as such.[30] In June, the World Health Organization (WHO) and US Centers for Disease Control (CDC) stopped counting cases and declared the outbreak to be a pandemic.[31]

Currently, there are 14,286 confirmed deaths worldwide. This figure is a sum of confirmed deaths reported by national authorities; the WHO states that total mortality (including deaths unconfirmed or unreported) from the new H1N1 strain is "unquestionably higher".[32]

The pandemic began to taper off in November 2009, [33] and by May 2010, the number of cases was in steep decline. [32][34][35][36] On 10 August 2010, the Director – General of the World Health Organization, Margaret Chan, announced the end of H1N1

pandemic.[37] Chan noted that the H1N1 pandemic could have been much worse. According to the latest World Health Organization statistics, the virus has killed more than 18,000 people since it appeared in April 2009,[38] approximately 4% of the 250,000 to 500,000 annual influenza deaths.[39]

MATERIALS AND METHODS

SETTINGS

Outpatient clinics at

- Institute of Internal Medicine

  Madras Medical college and Government General Hospital

  Chennai – 600003

- Department of Thoracic Medicine

  Madras Medical college and Government General Hospital

  Chennai – 600003

ETHICAL COMMITEE APPROVAL

Obtained

STUDY DESIGN

Cross sectional study design

PERIOD OF STUDY

September 2009 to October 2010

SAMPLE SIZE

50 cases

CONSENT

Informed consent was obtained from all the patients participating in the study.

INCLUSION CRITERIA

Patients who were treated for H1N1 influenza in Institute of Internal Medicine in Government General Hospital, Chennai 03, during the year 2009.

EXCLUSION CRITERIA

1. Patients with a history URI or LRI within previous 6 to 8 weeks duration
2. Smokers,
3. Patients who are not willing for spirometry testing.

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METHODOLOGY

Out of 58 patients initially enrolled for the study, 50 patients were selected. Others were excluded as per the exclusion criteria.

Patients previous records were reviewed to classify them according to WHO severity classification.

Patients were assessed for the presence symptomatology suggestive of air way diseases like cough, expectoration, breathlessness, wheeze, limitation of activities and exacerbation of their underlying illness .

They have also examined for the presence of signs of airway diseases like tachypnea, cyanosis, wheeze or rhonchi.

Subsequently the patients were subjected to pulmonary function test by spirometry.

SPIROMETRY

Spirometry was performed using standard equipment at the outpatient department of Thoracic Medicine. Airway indices like FEV1, FVC, FEV1/FVC and PEF were recorded in these patients.

The performance of spirometry while seated upright in a chair is preferable to standing as this is the most stable position should the patient experience dizziness during the test. The seated position is also preferable for patients with urinary incontinence who may otherwise limit the expiratory effort.

The key steps are to urge the patient to:[40][41][42]

- Breathe in fully (the lungs must be absolutely full).
- Seal the lips around the mouthpiece and immediately….
- Blast the air out as fast and as far as possible until the lungs are completely empty.
- Repeat the test until three acceptable and reproducible results are obtained (up to a maximum of 8 efforts)
- The highest FEV_1 and FVC should be reported, even if they come from separate blows.

Spirometry requires maximal effort from the patient and it takes time to perform quality spirometry. As it was essential the procedure was carefully and clearly explained to the patient and motivated to perform maximally and completely. The volume and flow parameters measured are defined in terms of maximal effort and maximal exhaled volume.

While it is not mandatory to use nose clips to prevent loss of measured volume through the nose , their use is sometimes of benefit.

Activities that should preferably be avoided prior to lung function testing

Smoking within at least 1 h of testing

Consuming alcohol within 4 h of testing

Performing vigorous exercise within 30 min of testing

Wearing clothing that substantially restricts full chest and abdominal expansion

Eating a large meal within 2 h of testing

Results

Acceptable results are those that were initiated at full lung inflation, and with maximum expiratory effort (eg no hesitation at the start and no pauses throughout the blow) until no more air can be expired. The results are reproducible if there is less than 200ml variation in FEV_1 and FVC between the two best blows.

Conditions where suboptimal lung function results are likely

Chest or abdominal pain of any cause

Oral or facial pain exacerbated by a mouthpiece

Stress incontinence

Dementia or confusional state

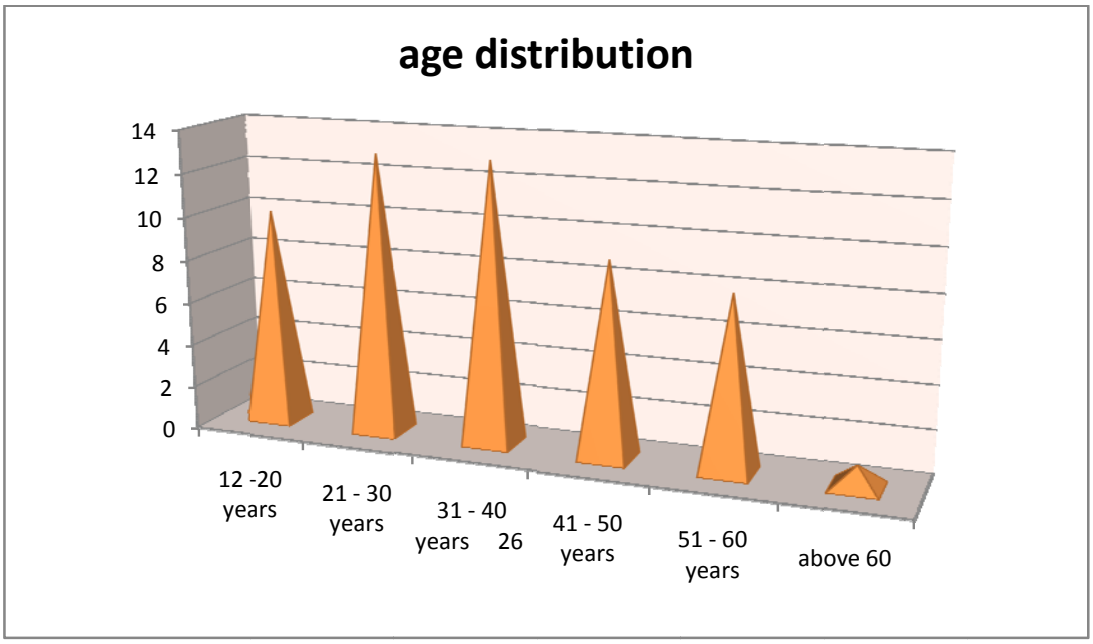
Severity of the airway obstruction:

- Mild - FEV1 > 80% of predicted
- Moderate - FEV1 50 – 80% of predicted
- Severe - FEV1 < 50% of predicted

RESULTS

AGE DISTRIBUTION

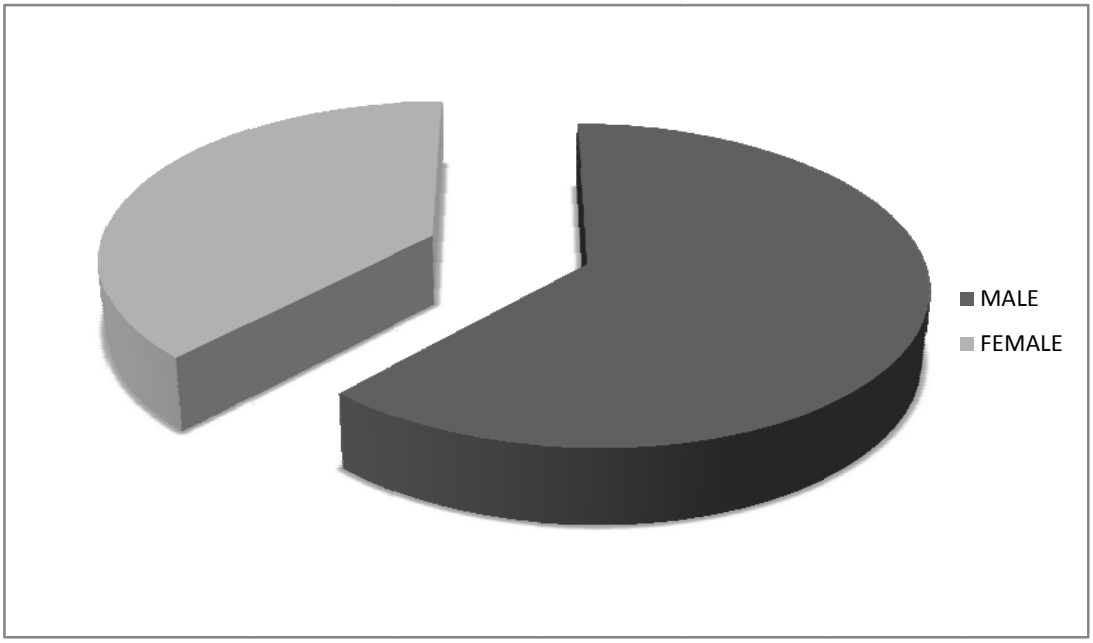
AGE GROUP	NO OF PATIENTS	PERCENTAGE
12 – 20 years	10	20%
21 – 30 years	13	26%
31 – 40 years	13	26%
41 – 50 years	09	18%
51 – 60 years	04	08%
Above 60 years	01	02%



The mean age of the study population is 32.92 years. Most of the patients are between 21 to 40 years of age.

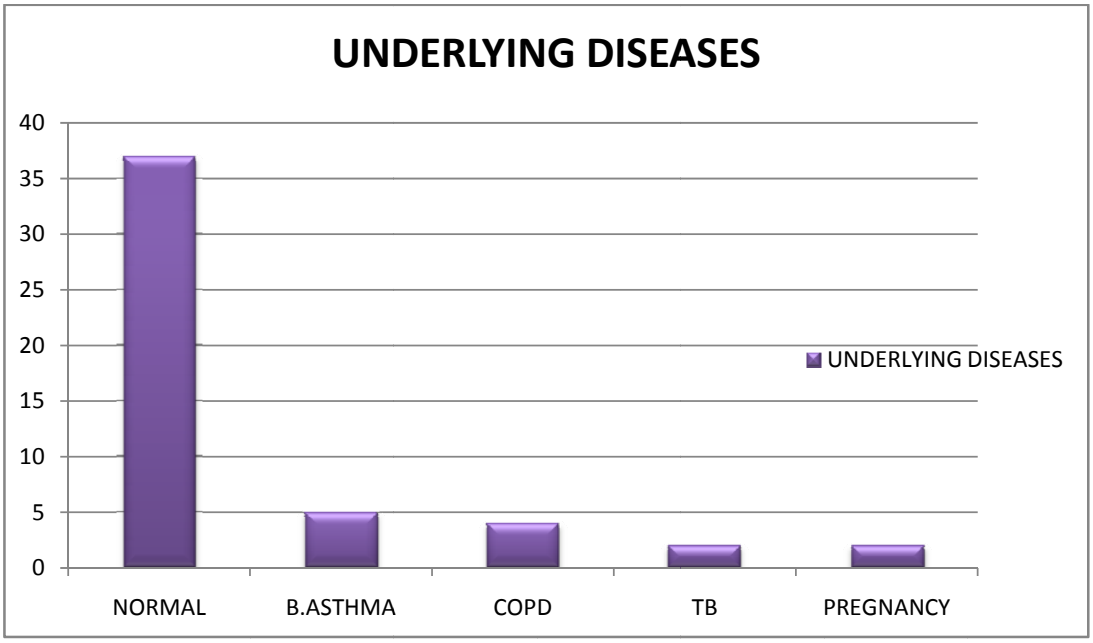
SEX DISTRIBUTION

SEX	NO OF PATIENTS	PERCENTAGE
MALE	31	62%
FEMALE	19	38%



UNDERLYING DISEASES

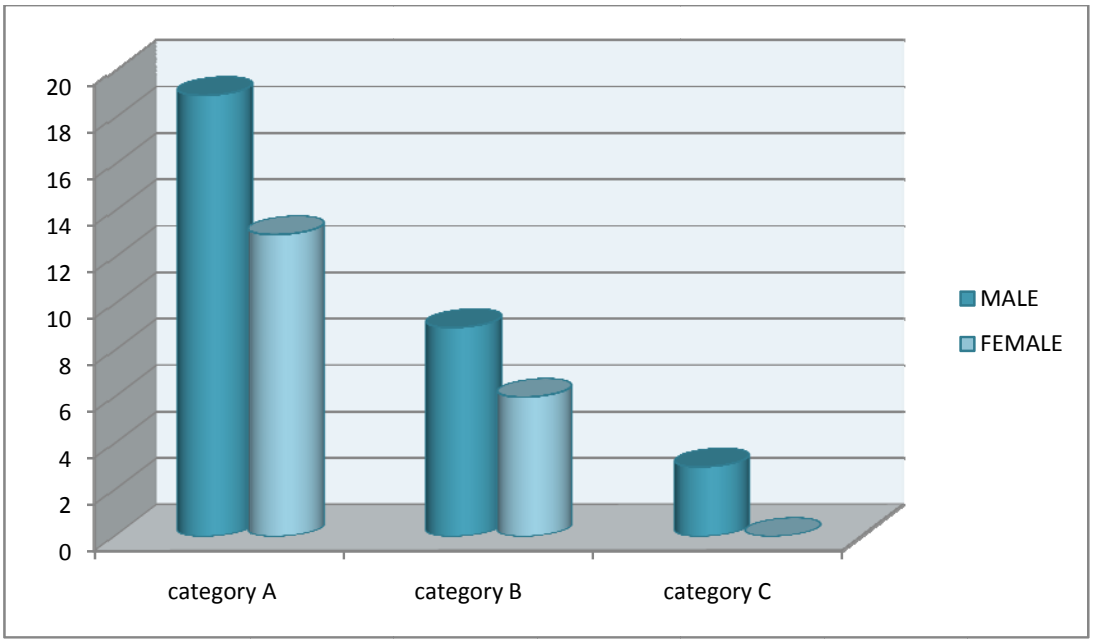
DISEASE	MALE	FEMALE	TOTAL	PERCENTAGE
B.ASTHMA	03	02	05	10%
COPD	04	-	04	08%
TUBERCULOSIS	02	-	02	04%
PREGNANCY	-	02	02	04%
NORMAL	22	15	37	74%



Most of the patient participated [around 74%] were having no underlying lung disease.

CLINICAL SEVERITY OF THE INFECTION

SEVERITY	MALE	FEMALE	TOTAL	PERCENTAGE
CATEGORY A	19	13	32	64%
CATEGORY B	09	06	15	30%
CATEGORY C	03	-	03	06%



The majority of the patients in this study were H1N1 positive

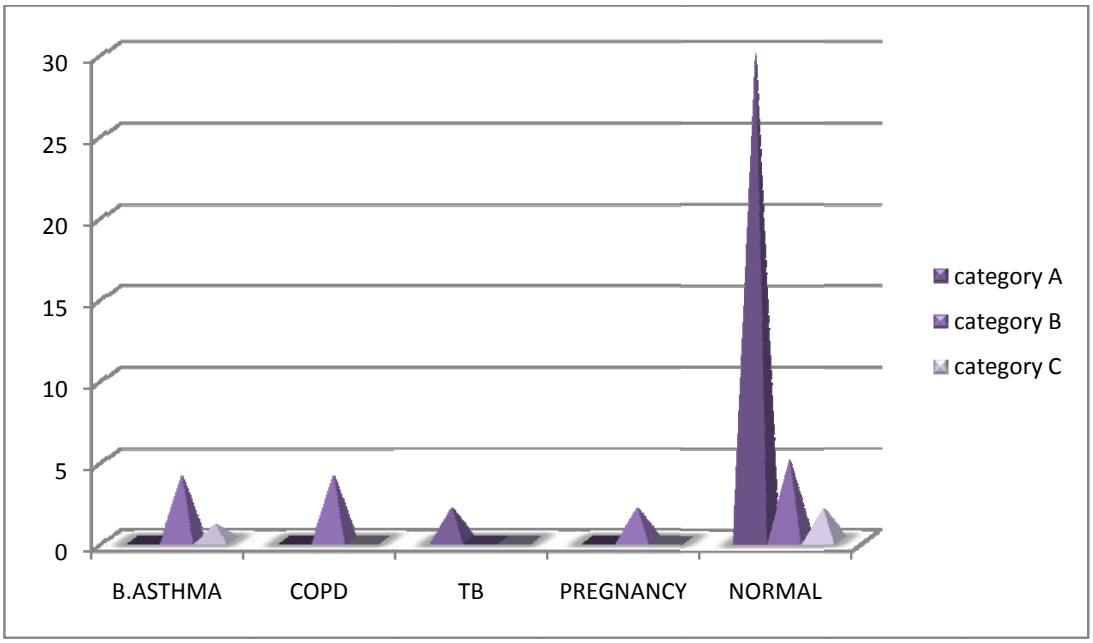
category A i.e, 64%

30% category B

06% category C

CLINICAL SEVERITY AND UNDERLYING DISEASE

UNDERLYING DISEASE	CATEGORY A	CATEGORY B	CATEGORY **C**	TOTAL
B.ASTHMA	-	04	01	05
COPD	-	04	-	04
TUBERCULOSIS	02	-	-	02
PREGNANCY	-	02	-	02
NORMAL	30	05	02	37



Patients with underlying lung diseases experienced severe grade of infections as compared to individuals with normal lung.

Females who were pregnant during the acute illness had experienced severe involvement of lung.

CLINICAL PRESENTATION

DISEASE	NO OF PATIENTS	RECURRENT RTI	WHEEZE	TOTAL
B.ASTHMA	05	04	04	04
COPD	04	02	02	02
TUBERCULOSIS	02	-	-	-
PREGNANCY	02	-	-	-
NORMAL	37	-	-	-

Non of the patients with normal lung prior to H1N1 influenza had experienced any increase in the incidence of respiratory infections or new onset of breathlessness or wheeze.

Patients who was treated for pulmonary tuberculosis previously and females who were pregnant during the influenza infection have not developed any new symptoms.

Out of five bronchial asthma patients who participated in the study four patients experienced increase in the episodes of acute exacerbation of their symptoms.

Out of four COPD patients in the study two patients had more frequent exacerbation of their symptoms.

BRONCHIAL ASTHMA AND H1N1 INFLUENZA

Patients	Age/ Sex	No of years of illness	Exacerbations /yr before H1N1	H1N1 severity	Exacerbations after H1N1	No of hospital admission	spirometry
Pt – 1	15/M	6 years	1	B	4	2	Obstructive pattern
Pt – 2	29/M	15 years	2	C	4	4	Obstructive pattern
Pt – 3	20/M	8 years	1	B	2	1	Obstructive pattern
Pt – 4	21/F	8 years	1	B	3	1	Obstructive pattern
Pt – 5	31/F	11 years	1	B	-	-	Obstructive pattern

Four patients experienced a significant increase in episodes of acute exacerbations and all the patients who experienced increase in acute exacerbations required at least one hospital admission for the management of their symptoms.

Patient who had severe disease had severe grade of infection during H1N1 influenza and had experienced 4 episodes of acute exacerbation of bronchial asthma.

COPD AND H1N1 INFLUENZA

S. NO	Age/ Sex	No of years of illness	Exacerbations/ yr before H1N1	H1N1 severity	Exacerbations after H1N1	No of hospital admission	spirometry
1.	53/ M	4	2	B	2	-	Obstructive pattern
2.	53/ M	6	4	B	6	2	Obstructive pattern
3.	36/ M	2	1	B	3	1	Obstructive pattern
4.	49/ M	2	1	B	1	-	Obstructive pattern

Out of four patients two had increase in the episodes of acute exacerbation of their symptoms and both of them required hospitalization at least once.

EFECTS OF H1N1 INFLUENZA ON NORMAL LUNG

	Category A	Category B	Category C	Total Patients	Symptoms	spirometry
Male	19	02	02	23	Nil	Normal pattern
Female	11	05	-	15	Nil	Normal pattern

All the patients who were treated for H1N1 influenza had no new respiratory symptoms like breathlessness or wheeze independent of severity of their H1N1 infection.

Two females who were pregnant during H1N1 infection had normal ante partum period and normal child birth after treatment with oseltamavir.

DISCUSSION

Summary

This is a cross sectional study of patients who were previously diagnosed positive for H1N1 influenza and treated in government general hospital. Totally 58 patients were participated in the study out of them 50 were selected based on the exclusion criteria and subjected to retrospective history regarding the respiratory symptoms, clinical examination of the respiratory system and spirometry. All the patients in this study were had the disease (H1N1 influenza) one year prior to the study.

As compared to the previous studies which was conducted during the H3N2 influenza[43] patients were had an interval of one year between the illness and the study and the patients in that study were tested for pulmonary functions along with above measures they have used oscillatory method[44] for assessing airway resistance.

Characteristics of the study population

The age distribution of the study population is distributed widely from 13 years to 61 years . And the average age of the study population in the present study is 32.92. Most of the patients were in the age group between 21 to 40 years of age.

Around 62% percent of the population participated in the population were males.

Out of 50 patients participated in this study five patients were asthmatics, four patients were had COPD, two patients were previously treated for pulmonary tuberculosis and two females were pregnant during the time of H1N1 infection.

Two pregnant females had normal ante partum period and normal labour.

Patients with underlying lung disease experienced severe form of lung disease when compared to the people with no underlying lung disease.

Patients with underlying lung disease like bronchial asthma and COPD experienced increase in the episodes of acute exacerbations when compared to pre H1N1 infection period.

People with underlying normal lung function and with no other precipitants does not developed any new symptoms or any derangement in lung functions.

CONCLUSION

1. H1N1 influenza infection does not produced any persistent symptoms or signs of impaired pulmonary fuctions in individuals who had normal lung function prior to H1N1 influenza infection.

2. Patients who had pulmonary tuberculosis and completed treatment and no residual anatomical damage also did not have persistent defect in lung functions.

3. Patients with COPD and bronchial asthma showed an increase in the frequency of acute exacerbations after H1N1 influenza infection which persisted more than a year.

Hence it may be inferred that patients with diseased airways like COPD and bronchial asthma had severe disease during the acute stage of H1N1 influenza infection and are more susceptible for increased hyper responsiveness of the bronchial airways which may be become persistent.

SUGGESTIONS

Since the patients with underlying lung diseases like COPD and Branchial Asthma experienced severe infection during the acute phase and had persistent deterioration of there underline lung disease after H1N1 influenza infection. So this patients should be vaccinated against influenza infection.

ABBREVIATIONS

COPD – Chronic Obstructive Pulmonary Disease

RSV - Respiratory Syncytial Virus

ICAM-1 - Intercellular Adhesion Molecule 1

TNF – Tumor Necrosis Factor

AHR – Airway Hyper Responsiveness

IL – Interleukin

GM-CSF – Granulocyte Monocyte Colony Stimulating Factor

ECP – eosinophil cationic proteins

MIP-1alpha – macrophage inflammatory protein

RTI – Respiratory Tract Infections

ARDS – Acute Respiratory Distress Syndrome

PFT – Pulmonary Function Test

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PROFORMA

Name: **Age/Sex**:

Address:

Complaints during H1N1 infection:

Sore throat : Yes/ No

Cough with expectoration: Yes/ No

Fever : Yes/ No

Breathlessness : Yes/ No

Hemoptysis : Yes/ No

Other symptoms :

Hospital admission : Yes/ No

Methyl prednisone : Yes/ No

Present complaints;

Persistent symptoms

Cough : Yes/ No **Expectoration:** Yes/ No

Breathlessness : Yes/ No **Wheeze** **:** Yes/ No

Limitation of activities : Yes/ No

Other symptoms :

Past History :

COPD : Yes/ No

Bronchial asthma : Yes/ No

Connective tissue disease: Yes/ No

Tuberculosis : Yes/ No

Personal History:

Smoking : Yes/ No Duration:

Occupational exposure to respiratory pollutantants: Yes/ No

Examination :

Cyanosis: Yes/ No **Pallor**: Yes/ No

Clubbing: Yes/ No

Respiratory system

Sings of volume loss : Yes/ No

Auscultation :

Breath sounds :

Wheeze : Yes/ No localized / generalized

Crepitations : Yes/ No

Investigations :

Chest X ray:

Trachea :

Lung fields :

Others :

Complete blood count:

TC :

DC : P: L: E:

ESR :

Hb :

PCV :

Platelets :

Pulmonary function test:

Tidal volume :

TLC **:**

FEV1 **:**

FVC **:**

FEV1/ FVC **:**

Outcome:

Follow-up:

MASTER CHART

S. NO	AGE / SEX	RECU RRENT RTI	WHE EZE	B.AST HMA	COPD	TB	PREGN ANCY	SIGNS	X-RAY	FEV1	FVC	FEV1/ FVC	INFERENC E
1.	23/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	106	105	105	Normal Study
2.	49/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	84	76	118	Normal Study
3.	55/m	Nil	Nil	Nil	Nil	YES		Nil	Normal Study	99	115	91	Normal Study
4.	24/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	100	98	102	Normal Study
5.	18/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	90	109	Normal Study
6.	15/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	102	100	102	Normal Study
7.	42/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	100	106	94	Normal Study
8.	19/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	102	101	101	Normal Study
9.	50/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	96	98	98	Normal study
10.	14/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	100	95	105	Normal Study
11.	61/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal study	100	106	94	Normal Study

S. NO	AGE / SEX	RECU RRENT RTI	WHE EZE	B.AST HMA	COPD	TB	PREGN ANCY	SIGNS	X-RAY	FEV1	FVC	FEV1/ FVC	INFERENC E
12.	50/m	Nil	Nil	Nil	Nil	YES		Nil	Normal study	98	90	109	Normal Study
13.	50/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	89	90	99	Normal Study
14.	29/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	92	100	92	Normal Study
15.	22/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	105	98	107	Normal Study
16.	46/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	92	96	96	Normal Study
17.	14/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	97	101	Normal Study
18.	37/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	100	98	102	Normal Study
19.	15/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	90	109	Normal Study
20.	27/f	Nil	Nil	Nil	Nil	Nil	YES	Nil	Normal Study	99	115	91	Normal Study
21.	40/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	99	98	101	Normal Study
22.	20/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	102	96	Normal Study
23.	13/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	102	105	97	Normal Study

S. NO	AGE / SEX	RECU RRENT RTI	WHE EZE	B.AST HMA	COPD	TB	PREGN ANCY	SIGNS	X-RAY	FEV1	FVC	FEV1/ FVC	INFERENC E
24.	21/ f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	92	106	Normal Study
25.	30/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	101	98	103	Normal Study
26.	34/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	89	99	90	Normal Study
27.	37/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	97	101	Normal Study
28.	19/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	105	98	107	Normal Study
29.	30/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	92	96	96	Normal Study
30.	54/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	97	101	Normal Study
31.	23/f	Nil	Nil	Nil	Nil	Nil	YES	Nil	Normal Study	100	98	102	Normal Study
32.	26/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	90	109	Normal Study
33.	32/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	89	90	99	Normal Study
34.	33/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	92	100	92	Normal Study
35.	27/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	89	99	90	Normal Study

S. NO	AGE / SEX	RECURRENT RTI	WHEEZE	B.ASTHMA	COPD	TB	PREGNANCY	SIGNS	X-RAY	FEV1	FVC	FEV1/ FVC	INFERENCE
36.	27/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	97	101	Normal Study
37.	40/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	105	98	107	Normal Study
38.	15/m	YES	YES	YES	Nil	Nil		wheeze	Normal Study	90	106	84	Normal Study
39.	31/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	84	76	118	Normal Study
40.	29/m	YES	YES	YES	Nil	Nil		wheeze	Normal Study	84	98	85	Normal study
41.	31/f	Nil	Nil	YES	Nil	Nil		wheeze	Normal Study	92	105	88	Normal Study
42.	34/m	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	97	101	Normal Study
43.	40/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	100	98	102	Normal Study
44.	50/f	Nil	Nil	Nil	Nil	Nil		Nil	Normal Study	98	90	109	Normal Study
45	20/f	YES	YES	YES	Nil	Nil		wheeze	Normal Study	76	100	76	Obstructive pattern
46.	21/m	YES	YES	YES	NIL	Nil		wheeze	Normal Study	78	98	79	Obstructive pattern
47.	53/m	Nil	Nil	Nil	YES	Nil		Nil	Emphysematous	53	92	57.6	Obstructive pattern

S. NO	AGE / SEX	RECU RRENT RTI	WHE EZE	B.AST HMA	COPD	TB	PREGN ANCY	SIGNS	X-RAY	FEV1	FVC	FEV1/ FVC	INFERENC E
48.	53/m	YES	YES	Nil	YES	Nil		Nil	Emphyse matous lung	60	88	68.18	Obstructiv e pattern
49.	36/m	YES	YES	Nil	YES	Nil		Nil	Emphyse matous lung	55	88	62.5	Obstructiv e pattern
50.	49/m	Nil	Nil	Nil	YES	Nil		Nil	Emphyse matous lung	62	80	77.5	Obstructiv e pattern