"CLINICAL PRESENTATION AND IMPULSE OSCILLOMETRY TO DIFFERENTIATE BETWEEN WHEEZING EPISODE AND PNEUMONIA IN CHILDREN"

A

Thesis

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D. Y. Patil Education Society, Kolhapur

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For the Degree of

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IN

PAEDIATRICS

By

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KOLHAPUR – 416 006

(2021)

DECLARATION

I hereby declare that the work containing in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institute in India or any other country. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made. Further, I declare that I have not violated any of the provisions under Copyright and piracy / Cyber / IPR Act amended from time to time.

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RESEARCH PUBLICATIONS (11)

Dr. Suhas Kulkarni, Associate Professor, Department Of Pediatrics, D. Y. Patil Medical College, Kolhapur.

1) Kamatkar M, Kulkarni S. P., Delayed hypersensitivity reaction type IV following intradermal vaccination an economic tool to study CMI: Study of 518 cases in rural pediatric population of 0-5 years for hepatitis B., Indian J Pathol Microbiol2007, vol 50 (supplement)
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RESEARCH PAPERS SENT FOR PUBLICATIONS (5)

1) Jaiswal JP, Kulkarni SP, Comparative Evaluation of the Efficacy of Nasal Mask CPAP versus Nasal Prong CPAP for the Treatment of Neonatal Respiratory Problems.
2) Kulkarni SP, Kurane A, Prevalence of Asthma and Associated Risk Factors in Rural Children of Karveer Taluka,
3) Jaiswal JP, kulkarni SP, Susmitha NV and Patil M, The MIS-C dilemma in 2 cases.
4) Kulkarni SP, Case report of Dengue encephalitis.
5) Kulkarni SP, Kurane AB, Wheezing in Preschool Children: New Perspective (review article).

CONFERENCES ATTENDE: PEPPER / POSTER PRESENTATION

1) Respicon 2018, Indian Academy of Pediatrics, Indore 23-24th November 2018. Presented research paper as a poster. Kulkarni SP, Kurane A, Prevalence of Asthma and Associated Risk Factors in Rural Children of Karveer Taluka.

2) 5 th international conference "Angiogenesis Research: Targeted Anti-angiogenic Therapy" Oral paper presentation. D. Y. Patil education society (Deemed to be University, Kolhapur).

3) 35th International Conference on Advanced Pediatrics and Neonatology 23 November 2020. Oral presentation on respiratory problems and use of impulse oscillometry in children 3 years to 6 years old. (Webinar)

Conferences attended as delegate and faculty (60)		
1	07-September-13	Reviewer panel on “paediatric on call” e journal, Mumbai
2	19 & 20 April 2014	AIIMS paediatric pulmonology & intensive care course (Module 1 - Pulmonary Physiology) Delegate
3	1 & 2 November 2014	26TH RESPICON, Varanasi (IAP respiratory chapter)Delegate
4	19th & 20th January2015	D. Y. Patil Education society(Deemed to be University) workshop on "application of statistics in medical research" delegate
5	April.2015	S.T.A.B.L.E program (USA), Valley Children Hospital, Fresno, California USA, Delegate
6	05-July-15	Preparation and training of trainers "workshop on MINIRESPIRE module in IAP action plan 2015"tot delegate
7	5 & 6 September 2015	AIIMS, paediatric pulmonology & intensive care course (Module 4 - Asthma & Allergic Disorders)Delegate
8	23-August-15	STABLE workshop, IAP North Canara, Karnataka, Faculty
9	23 & 24 April 2016	AIIMS, paediatric pulmonology & intensive care course (Module V - Chronic Respiratory Disorders) Delegate
10	18, 19 & 20 November 2016	MAHAPEDICON 2016 Aurangabad, delegate
11	18, 19 & 20 November. 2016	Pre conference workshop & CME MAHAPEDICON 2016 Delegate
12	20-22nd December 2016	MUHS, Nashik, Revised basic course workshop MET Delegate
13	23-December 16	MUHS, NASHIK sensitization program for attitude & communication (AT-COM) module MET Delegate

14	18, 19 & 20 April 2017	Revised basic course workshop in medical education technologies, At D Y Patil medical college, Kolhapur Resource faculty
15	7th May 2017	IAP RNTCP paediatric tuberculosis module CME by Kolhapur Academy of Pediatrics, Delegate.
16	June-17	Membership certificate RRNI (Respiratory research network of India) Research paper at ERS conference.
17	1 & 2 July 2017	5th NATIONAL PED ALLERCON 2017 (Allergy and applied immunology chapter of IAP) at Hyderabad Delegate
18	13 August 2017	CME on Paediatric respiratory problems (as faculty) IAP GOA chapter 2017-18 Faculty
19	23 & 24 September 2017	5TH National conference on pediatric education (NCPE 2017) at Bharati Vidyapeeth University medical college, Pune delegate
20	28 & 29 October 2017	RESPICON 2017 (IAP national respiratory chapter) at Bangalore Delegate
21	6 October 2017	MAHANEOCON 2017 workshop BASIC NRP TOT (as faculty) by KAP.
22	06/10/2017	District instructor (BNCRP PART-1) course of IAP-NNF neonatal resuscitation program first golden minute project at kolhapur, as a faculty.
23	6, 7 & 8th October, 2017	Certificate of appreciation MAHANEOCON 2017 at Kolhapur, Organizer
24	2-3 January. 2018	Non-invasive ventilation workshop PEDICON 2018 Nagpur, Delegate.
25	5-7th January. 2018	PEDICON 18 Nagpur 55TH national conference of IAP Delegate and chairman for 2 lectures
26	22, 23 & 24 February 2018	3T-IBHSc training course for health science faculty' under the Indian program of the UNESCO chair in bioethics (Haifa) Delegate
27	25-February18	STEER COURSE BY Kolhapur Academy of Pediatrics, delegate
28	5th - 9th March 2018	MCI 6th session advance course in Medical Education Technology, delegate
29	18-May-18	Speaker on CME on under 5 wheezing
30	23th & 24th June 2018	Advanced pulmonary function testing workshop by Chest Research Foundation Pune
31	August-18	International Certificate on Principles of bioethics and Human Right by UNESCO Chair Bioethics Haifa (6 months course online)

32	September-18	D. Y. Patil Education Society,(Deemed to be University) Kolhapur "good clinical practices guideline & schedule for clinical trial" Delegate, Conducted by department of pharmacology and therapeutics Seth G.S. Medical College, Mumbai
33	September-18	KAPCON 18 BY Kolhapur Academy of Pediatrics Delegate
34	October-18	D.Y.Patil Education society, Kolhapur 5th international conference "Angiogenesis Research: Targeted Anti-angiogenic Therapy " Oral paper presentation
35	23 TO 26 October 18	SETH GSMC, MCI Nodal centre workshop on AET at D.Y.Patil medical college, Kolhapur.
36	23-November-18	RESPICON 2018 Workshop on bronchoscopy, Indore Delegate
37	24 & 25 November 18	POSTER PRESENTATION in RESPICON 18, ON prevalence of asthma & asthma like symptoms in children in rural area of Karveer
38		RESPICON 2018 Indore MP Delegate
39	December-18	Paed Allercon 18 6th annual conference Chennai Faculty
40	17-January-19	D. Y. Patil, Kolhapur gave lecture on "professionalism organized by dept of biochemistry D.Y Patil Medical College, Kolhapur
41	October 2019	Word bioethics day by D. Y. Patil University organizing team
42	July 2019	RNTCP updated TB paediatric guidelines 2019 by IAP & SAATHI Mumbai Training of Trainers
43		IAP, NNF FIRST GOLDON MINUTE workshop AS Faculty, BNCRP Part 1 Faculty
44	September-19	KAPCON 19 by Kolhapur academy of paediatrics Delegate
45	October-19	RESPICON 2019 AT PUNE Delegate
46	24-November-19	COMHAD 19 Kolhapur, faculty & delegate at D.Y.Patil Medical College, Kolhapur and organizer(treasurer)
47	December-19	Artificial Intelligence & MED APP ON 12 DEC 19 AT D. Y. Patil, Kolhapur, Organizer and delegate
48	December 2020	Basic Course in Biomedical Research by ICMR/NIE 91% score
49	February-20	IABSCON, dept. Biochemistry 2020 D. Y. Patil Kolhapur, in 9 th annual international conference of biomedical sciences, speaker
50	07-Feb-20	Seth G.S. Medical College & KEM hospital ADVANCE COURSE IN MEDICAL EDUCATION

		completed 7th February 2020
51	2019	Indian Academy of Pediatrics: Respiratory chapter: Life membership No. R/2019/K-140
52	09-june-2020	Asthma key concepts useful in office practice, National webinar, speaker
53	31-July-2020	Pediatric Allergy demystified II, National Webinar, Panellist
54	27-28th September 2020	Odisha State Respicon 2020 Delegate
55	29-September-2020	Relooking controller therapy for pediatirc asthma-in realm of GINA 2020 Webinar, speaker
56	27-November-20	Indian Academy of Pediatrics: Respiratory chapter: Cough Approach and Management(CAMP) module in Pediatrics Training of the Trainers(TOT)
57	23-November-20	35th International conference on Advanced Pediatrics and Neonatology, Oral paper presentation Respiratory problems and use of impulse oscillometry in children 3years to 6 years
58	29-November-20	Indian Academy of paediatrics: National Respiratory Chapter Judge in PG case presentation competition
59	December-20	SIMULCON 2 nd national conference virtual workshop
		Qualitative Research in Healthcare Simulation
60	25th and 26th March 2021	Indian Academy Of Pediatrics First national Training of trainers on “Dysbiosis Module “(central IAP certified trainer)

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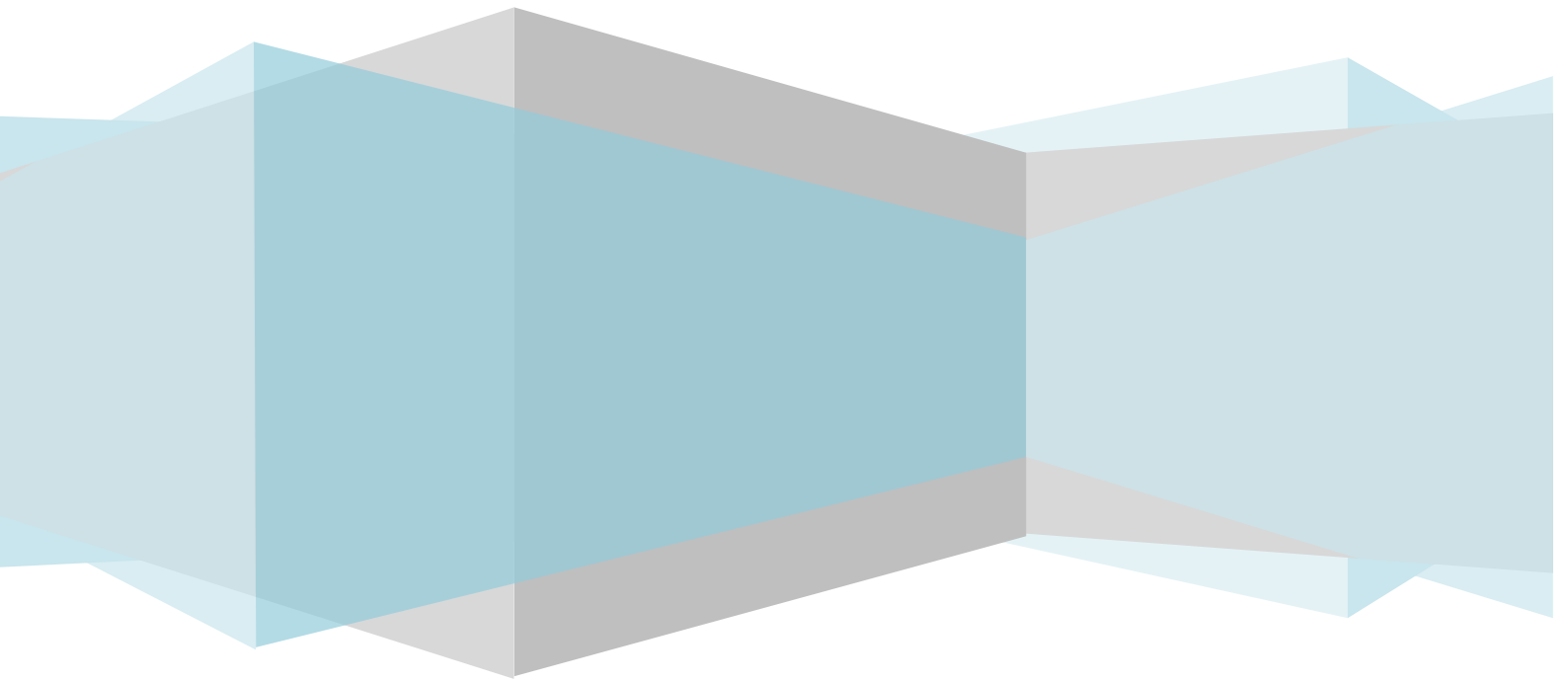
LIST OF ABBREVIATIONS

- AHR: Airway Hyper Responsiveness
- ALSPAC: Avon Longitudinal Study Of Parents And Children
- ALRI: Acute Lower Respiratory Tract Infection
- API: Asthma Predictive Index
- ARI: Acute Respiratory Infection
- ATS: American Thoracic Society
- AX: Reactance Area
- CAPPS: Canadian Asthma Primary Prevention Study
- ERS: European Respiratory Society
- FeNO: Fractional Exhaled Nitric Oxide
- FRC: Functional Residual Capacity
- FVC: Forced Vital Capacity
- FEV1: Forced Expiratory Volume in One Second
- FOT: Forced Oscillation Technique
- GINA: Global Initiative for Asthma
- $G_{AW:}$ Airway Conductance
- ICS: Inhaled Corticosteroids
- IMCI: Integrated Management Of Childhood Illness
- IOS: Impulse Oscillometry System
- ISAAC: International Study on Asthma and Allergy in Children
- LCI: Lung Clearance Index
- MAC: multizentrische Allergistudie
- MeDALL: Mechanism Of Development Of Allergy
- PASTURE: Protection Against Allergy: Study In Rural Environment
- PIAMA: The Prevention And Incidence Of Asthma And Mite Allergy

- PEF: Peak Expiratory Flow
- R at 20 Hz: Respiratory Resistance Measured At 20 Hz Frequency
- R at 5 Hz: Respiratory Resistance Measured At 5 Hz Frequency
- Res Fr: Resonant Frequency
- Rrs: Respiratory Resistance
- RSV: Respiratory Syncytial Virus
- SABA: Short Acting Beta 2 Agonist
- SpO2: Fraction Of Haemoglobin Carrying Oxygen In Blood
- sRaw: Specific Airway Resistance
- sGaw: Specific Airway Conductance
- TAA: Thoraco-Abdominal Motion Wall Analysis
- URECA: Urban Environment And Childhood Asthma
- URTI: Upper Respiratory Tract Infection
- Vbe: Backward Extrapolated Volume
- WHO: World Health Organization
- X at 20 Hz: Reactance Measured At 20 Hz Frequency
- X at 5Hz: Reactance Measured At 5 Hz Frequency
- (Xrs): Respiratory Reactance
- Z at 5 Hz: Respiratory Impedance Measured At 5 Hz Frequency
- (Zrs): Respiratory Impedance

CHAPTER-I
INTRODUCTION



INTRODUCTION

Respiratory problems are the commonest cause of morbidity and mortality in children. As the infective causes due to bacterial infections are decreasing, the respiratory problems due to viral infections and allergies are increasing relatively. The diagnosis of this condition objectively is difficult due to non-availability of a test which can be performed in children easily. In small number of children, however wheezing episodes may have predisposition to asthma.[1]

Measurement of lung function is an important investigation in arriving at a diagnosis of obstructive airway diseases. It helps in making a specific diagnosis, choosing medications and assessing prognosis. It can also help in monitoring response to therapy.

Spirometry is the currently preferred test for assessing pulmonary function in regular office practice and is considered to be investigation of choice for diagnosing asthma. However spirometry is difficult because it requires patient cooperation to perform forceful mannouvres. Children aged less than 5 years cannot perform the test routinely.

Du Bois et al[2] described the forced oscillation technique (FOT). In this technique lung function was measured by sending sinusoidal sound waves into the lungs. The sound waves were generated by a loud speaker. It measured respiratory impedance (Zrs) that is total resistance of lungs. The impedence included the respiratory resistance (Rrs) and respiratory reactance (Xrs). The parameters were measured over a multiple frequencies

(usually from 3-35Hz). The information about resistance of the airways is provided by Rrs. The Xrs gives information about capacitance and inertia of the lungs.

The important characteristic of this machine was it could be performed easily and It provided the resistance directly which was not given by spirometry.[2] Impulse oscillometry has been used to assess lung function in children with respiratory problems.[3- 6]

Inspite of scientific advances the reduction in mortality due to respiratory problem in children has not decreased. The reason for this respiratory mortality is not clearly established.

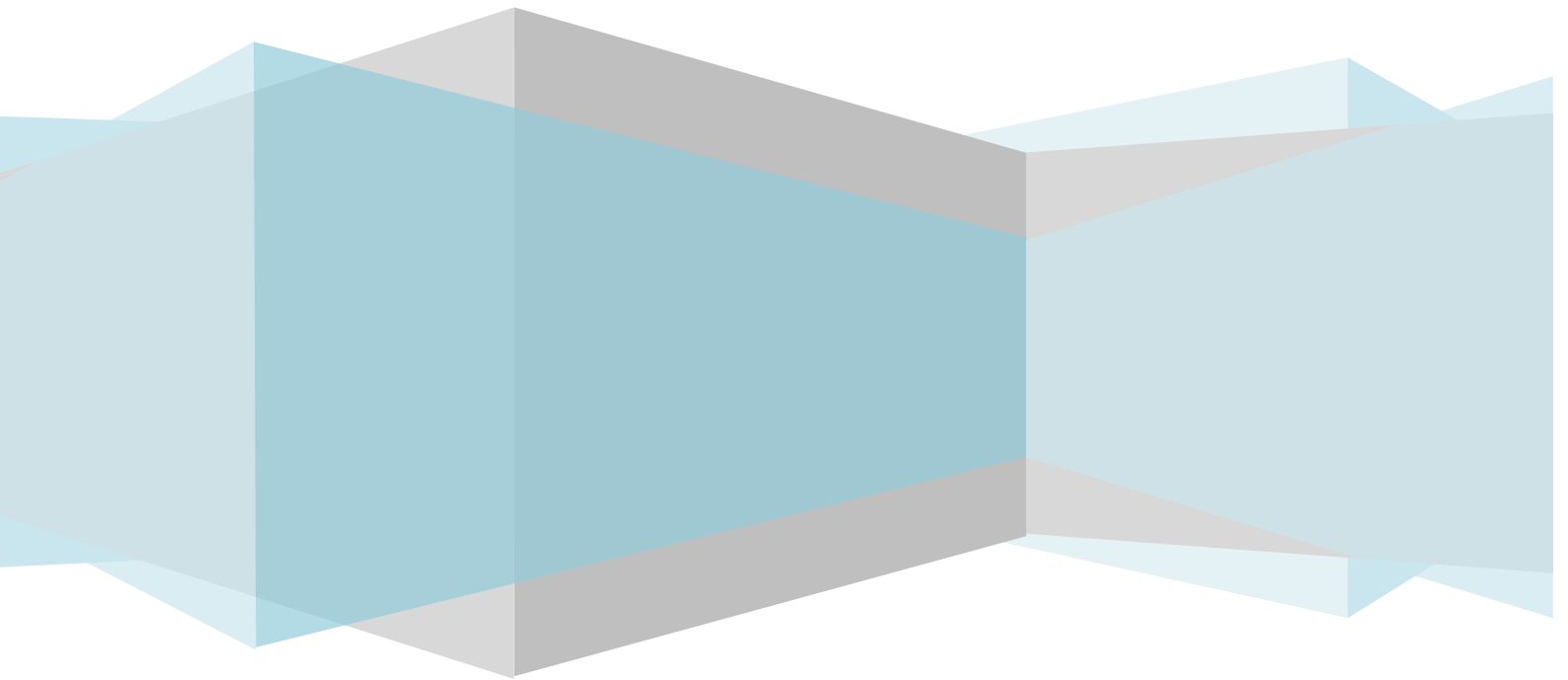
WHO has advised treatment of fast breathing children with antibiotics and treatment of severe pneumonia with chest indrawing with oral amoxicillin in high doses twice daily.[7]

It was observed that WHO guidelines which may over diagnose pneumonia and lead to overuse of antibiotics and may not be able to diagnose asthma and wheezing[7-11]. This has brought a need to clinically or otherwise differentiate between the pneumonia and wheezing episodes.[12,13] Most of the infants with wheezing below five years have transient conditions which may be associated with diminished airway function and the risk of asthma or allergy is very less.[14,15] WHO has advised three nebulizations in suspected cases of pneumonia and if there is improvement, label it as wheezing episode.[11] But there are patients which can be improperly treated with this approach also. It is better to have a scoring system or objective way of diagnosis. Marotta et al[3] observed that impulse oscillometry was better than spirometry in differentiating between

young children with asthma and without asthma when bronchodilator response was measured. Impulse oscillometry can be used in children above three years in diagnosis and management of lung diseases.[3-5]

A scoring system was developed to assess severity of respiratory illness.[12] Similarly a scoring system will be useful to differentiate between pneumonia and wheezing episode in 3 to 6 years old children. Skin prick test can be used to find allergic predisposition in children with wheezing.[16]

CHAPTER-II
AIM AND OBJECTIVES



AIM AND OBJECTIVES

AIM

Differentiation between wheezing episodes and pneumonia in 3-6 years old children with clinical presentation and pulmonary function testing with impulse oscillometry.

OBJECTIVES

1. Use of impulse oscillometry to differentiate between pneumonia and wheezing episode in 3-6 years old children.
2. To develop a scoring system to differentiate between wheezing episodes and pneumonia.

CHAPTER-III
LITERATURE REVIEW

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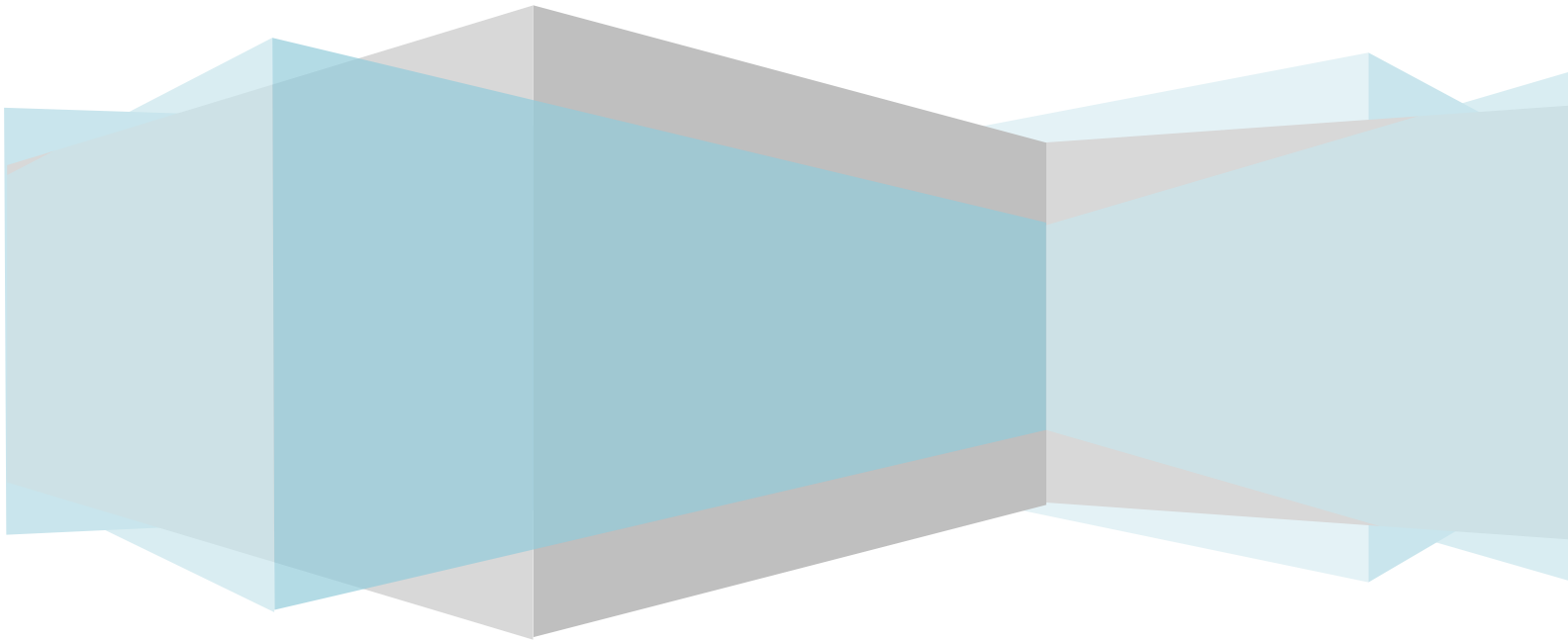


REVIEW OF LITERATURE

3.1 PNEUMONIA

3.1.1 Epidemiology

Pneumonia is an acute respiratory illness that affects the lung. Pneumonia is defined as inflammation of the lung parenchyma. The lungs are made up of alveoli. These alveoli are filled with air when normal healthy child takes a breath. In pneumonia these alveoli are filled with inflammatory cells. This causes breathlessness in a child. It limits oxygen intake in a child and leads to serious illness. It is the major cause of death among children with age less than 5 years. It leads to death in 1.2 million children every year. The incidence of pneumonia is 10 times more in developing countries. The number of deaths due to childhood pneumonia is 2000 times higher than developed countries.[17] Fifty percent of the mortality due to pneumonia in children less than 5 years occur in five countries.[18] In the last ten years, the child deaths decreased by 2 million in the whole world, with 40% decrease in overall reduction in deaths due to pneumonia and diarrhea. But still, pneumonia account for 1·3 million deaths and diarrheal disease cause 0·7 million deaths. Thus these two are major causes of infant deaths.[19] Decrease in burden of the pneumonia mortality and morbidity did not take place as has occurred with global child mortality. Incidence of diarrhea has decreased from 3·4 episodes to 2·9 episodes per child-year. The incidence of pneumonia has decreased from 0·29 episodes to 0·23 episodes per child-year between 1990 and 2010.[20,21]

In 2010, about 11.9 million episodes of severe pneumonia required hospital admission and 3 million episodes of very severe ALRI required hospital admission. Severe or very severe ALRI resulted in about 0·3 million deaths in hospitals in young children. Most of these deaths occurred in developing countries. Deaths in hospital were about 19%. 81% children died at home. In severe lower respiratory tract infections case fatality in hospital treated patients was very less as compared to children treated outside hospital.

The estimated hospital-based case-fatality ratio was 2·3% (95% CI 1·6–3·4) in children aged 0–59 months admitted with severe lower respiratory tract infections. The case fatality ratio was 6·1% (4·6–8·1) for those with very severe lower respiratory tract infection in developing countries.[22]

Furthermore, the findings suggest that even if improvement in access and care seeking behaviour of patients is achieved, the number of deaths may not decrease. In addition to strategies to increase coverage of pneumococcal vaccination in young children, improving community case management of childhood respiratory problems (including management of severe pneumonia by WHO) should be done. This will help in decreasing the remaining burden of mortality. It will remove the burden on hospital services, and improve the child mortality in low income countries.[18]

The oxygen treatment is required in 1.5 million children for hypoxemia in children admitted with lower respiratory tract

infections. This is because clinical signs are unable to diagnose hypoxemia.[22]

In this way 54% of diarrhea and 51% of pneumonia deaths in children younger than 5 years can be avoided by using these interventions up to 2025. However, significant improvement in interventions is likely to eliminate almost all diarrhea deaths, but it will improve only two-thirds of pneumonia deaths. Hence there is need to develop and implement more effective interventions for the prevention and treatment pneumonia.[18]

Unfortunately childhood deaths from pneumonia and diarrhea are not given importance worldwide as compared to HIV/AIDS or malaria.[22] Pneumonia was responsible for 15% childhood deaths. Actually it killed 808694 children in 2017.

3.1.2 Clinical Presentation

The clinical presentation of pneumonia varies according to pathogen, host and severity. No symptom or sign is pathognomonic in pneumonia in children. In infants and children symptoms and signs of pneumonia are not easily obvious. The presence of fever and cough together suggest pneumonia. The increased respiratory rate, increased work of breathing may appear earlier than cough. Cough is not a feature in initial phase of pneumonia as alveoli have less cough receptors. Cough starts when the inflammatory products irritate cough receptors in airways. The longer duration of fever and cough correlates with pneumonia. Abnormal breath sounds may not be present in infants, they may show restlessness, and they may not accept feeds and remain irritable. [7]

Diagnosis of pneumonia by clinical examination involves tachypnea, increased work of breathing associated with intercostal, subcostal and suprasternal retractions and nasal flaring. On auscultation of the chest crackels and wheezing may be heard but it is difficult to find out from which portion of the respiratory system these noises are heard in very young children. It is difficult to differentiate viral pneumonia from bacterial pathogens.[24]

The diagnosis of pneumonia is made by seeing infiltration on chest radiograph. Viral pneumonia usually shows hyperinflation of the chest, bilateral interstitial infiltrates and peribronchial cuffing. Lobar pneumonia is caused by pneumococci. The other features are also required to diagnose pneumonia and only radiologic features are not sufficient to diagnose pneumonia. Ultrasound examination of chest may be helpful in diagnosis of pneumonia.

White blood cell count may give some indication whether pneumonia is viral or bacterial.

To diagnose pneumonia WHO has decided criteria and according to that respiratory problems are graded as no pneumonia, pneumonia, severe pneumonia.[11] For this respiratory rate or chest in drawing are the criteria used. This strategy has helped to reduce deaths from pneumonia in many patients. In a systematic review by Rambaud-Althavs et al observed that the fast breathing when related with age (six studies; pooled sensitivity 0·62, 95% CI 0·26–0·89; specificity 0·59, 0·29–0·84) and chest in drawing (four studies; 0·48, 0·16–0·82; 0·72, 0·47–0·89**)** was not useful in the diagnosis as per the meta-analysis**.** They concluded that the criteria is insufficient

to diagnose pneumonia in children and addition of more clinical criteria or a point of care test is necessary to improve diagnosis of pneumonia.[25]

They also observed that single clinical features cannot diagnose pneumonia. Use of multiple clinical features can improve diagnosis. But point of care test would be useful to attain acceptable diagnostic accuracy.

The commonest organism causing pneumonia is streptococcal pneumonia in children below 5 years. In children 5 years and older mycoplasma pneumonie and chlmydophilla pneumonie are most common pathogens. Viruses such as RSV, parainfluenzae types 1, 2, 3, influenza A, B, Adenoviruses, Human metapneumovirus can give rise to pneumonia. The uncommon viruses are rhino virus, enteroviruses, herpes simplex virus, cytomegalovirus, measles and varicella also can cause pneumonia.

Deaths due to streptococcal pneumonie were 735000 and due to H influenzae type b were 363000 in 2000. They decreased to 541000 for streptococcal pneumonie and 203000 for H. Influenzae type b in 2008. The deaths decreased to 393000 for strep pneumonie and 59000 for H influenzae type b in 2015 according to a study by Wahl et al[26] published in lancet global health 2018.

Kumar et al[27] examined 100 children with respiratory problems and found that fever > 100 f had sensitivity of 88% and specificity of 76.4 % and a positive predictive value of 84.6. Leucocytosis had sensitivity of 72% and specificity of 100 % and positive predictive value of 100. Opacities on chest x-ray sensitivity of 100% specificity of 64.7% and positive predictive value 80.6.

They concluded that bronchopneumonia and bronchial asthma can be differentiated by history of fever, recurrence and leucocytosis.

In a review by Shah et al[28] twenty three prospective cohort studies of children (N=13833) with possible pneumonia no symptom was strongly suggestive of pneumonia. Vital signs fever (temperature >37.5 C (sensitivity 80-92%, specificity 47%-54%) and tachypnea (respiratory rate >40 breaths /min (sensitivity 79% specificity 51%) did not suggest pneumonia. Auscultatory findings also did not suggest pneumonia. Pneumonia was associated with moderate hypoxemia and increased work of breathing. Thus no single clinical finding suggested pneumonia as per the review.

In retrospective cross sectional study by Murphy et al[29] only fever was associated with pneumonia in 5.3% cases. Longer duration of cough and longer duration of fever more than five days and leucocytosis were associated with pneumonia.

Pleuritic chest pain may present in older children. But this finding is not common. In infants difficulty in feeding, restlessness may be only symptoms.

In children, fever is often present in pneumonia.[30] However, it is not very specific. In chlamydia pneumonia it may not be present. Fever is not present in asthma. It may be low grade in bronchiolitis. In some cases of pneumonia only symptom may be fever. It may be associated with leucocytosis but no clinical signs. 26% of 146 children less than five years with fever 39^0C and leucocytosis showed pneumonia on chest x-ray.[31] These children did not have any clinical evidence of pneumonia or other localizing signs

Tachypnea does not correlate well with chest x-ray evidence of pneumonia. Respiratory rate > 40 /min were associated 1.5 times

with chest x-ray showing pneumonia. Age appropriate rates of tachypnea were not associated with radiographic pneumonia.[28] Tachypnea may not be present in initial three days in cases of pneumonia.[28]

Signs of respiratory distress are tachypnea, hypoxemia (spo2 < 90%), increased work of breathing (use of accessory muscles, intercostal, subcostal or suprasternal, retractions, nasal flaring, grunting,), altered mental status.[30]

Hypoxemia is indicated by increased work of breathing and decreased level of activity. Hypoxemia indicates severe disease. Hence oxygen saturation should be measured in such cases. However pneumonia may be present without respiratory distress.

The signs of respiratory distress such as retractions, nasal flaring and grunting were seen more in radiographically confirmed pneumonia.[28]

3.1.3 Clinical examination

Examination of lung is useful in diagnosis of pneumonia and complications of pneumonia. The auscultatory findings suggest pneumonia. However auscultatory findings other than wheeze do not have inter- observer agreement. The observable findings such as retractions or respiratory rate have less inter observer variability.[32]

Clinical examination findings which suggest pneumonia on chest x-ray are, crackles and those suggestive of consolidation are decreased breath sounds, bronchial breath sounds, bronchophony (clear transmission of sounds such as one, one), whispering pectoriloquy, tactile fremitus and dullness to percussion.[33]

In pneumonia caused by atypical bacteria and viruses wheezing is more common. Korppi et al [34] tried to correlate clinical features and radiological features to identify viral, pneumococcal and atypical bacterial pneumonia but concluded that it was not helpful.

3.1.4 Radiological examination

Radiological evaluation: Normally chest x-ray is not required to treat uncomplicated lower respiratory tract infection which is usually treated in outpatient department.[35]

Indications for chest radiograph in children are to confirm diagnosis and assess complications. The indications are history of recurrent pneumonia, and in patients with pneumonia unresponsive to antimicrobial therapy. X-ray chest can help to exclude other possible diagnosis.[36]

But it has been observed that radiographic findings do not indicate etiological diagnosis and radiological findings should be used with other clinical features to treat the patients. The radiographic findings may not appear in initial few days.[35, 38]

It is also stated that 'children with a low clinical suspicion for pneumonia can safely be observed without chest-xrays'.[37] In a study by Swingler et al[38] it was found that the use of radiographs in children who were not hospitalized acute lower – respiratory infection did not reduce time to recovery or subsequent use of health facility. It was recommended that chest x-rays should be avoided routinely in this group of patients.

Clues to etiology: Classically bacterial pneumonia due to streptococcus pneumonie occurs days after upper respiratory tract

infection symptoms. In streptococcal pneumonia respiratory distress is moderate to severe and auscultation shows localized chest signs. Chest pain and signs and symptoms of sepsis are more suggestive of bacterial etiology.[37]

Atypical bacterial pneumonia due to Mycoplasma pneumonie or Chlamydia pneumonie shows following symptoms and signs. They are fever, headache, body ache, photophobia, sore throat and nonproductive cough which remains even after improvement in other symptoms.[38, 39]

3.2 Wheezing in children

3.2.1 Wheezing phenotypes

The first detail study about wheezing in children was carried out at Tucson by Martinez F.D. et al[1] and was published in 1995. In this study they analyzed the factors affecting wheezing in children before the age of 3 years and they were again examined at six years to know the relation to wheezing at that age.

1246 newborn were enrolled and data for 826 children was available at both three years and six years. The assessment involved questionnaire for parents, cord serum IgE levels and pulmonary function testing. Assessment at six years was done with serum IgE levels, pulmonary function testing and skin allergy testing. The results showed at the age of six years 51.1 percent did not have any episode of wheeze, 19.9 percent had at least one lower respiratory tract illness with wheezing but did not develop wheezing at six years of age. Fifteen percent did not have wheezing up to three years of

age and they developed wheezing at six years of age, 13.7 percent of children had wheezing before the age of three years of age and also at the age of six years.

The conclusion was that the children who had good prognosis were those who had wheezing in first three years of life. The children who had persistent wheezing had elevated serum IgE levels. Children developed reduced lung function that had persistent wheezing at the age of six years. It also indicated that the lung function was normal at one year of age but due to chronic process it decreased. Thus it indicated that it is necessary to identify the children with persistent wheezing below five years and to treat them[1].

Kurukulaaratchy et al[41] tried to characterize the wheezing phenotype in children less than 10 years. To examine natural history of childhood wheezing a birth cohort of 1456 was followed. It showed that 37% children who had wheezing by 4 years had wheezing even at 10 years of age. The children with persistent wheezing showed significantly more physician diagnosed asthma. They concluded that children with early onset of wheezing which is persistent are associated with more morbidity in first 10 years of life. Early onset persistent wheezing is related with with atopy, bronchial hyper responsiveness and impaired lung function. Late onset wheezers had lower chances of adverse health outcomes.

The European respiratory society's task force made it clear that wheezing in children less than five years should be differentiated from the term asthma as the patho-physiology of

wheezing in children is not similar to asthma in older children and adults. Phenotypes derived from epidemiological studies (transient versus persistent wheeze) should be used in retrospective way. This phenotypic classification has improved understanding about wheezing in children but it is not useful in clinical setting. It divided wheezing in children according to temporal pattern into two types. The first one is episodic wheeze which was defined as discrete episodes of wheezing and in between the child is normal. It is usually associated with viral infection. The viral infections which can lead to episodic wheeze were thought to be rhinovirus, respiratory syncytial virus (RSV), corona virus, and human metapneumovirus. Repeated episodes tend to occur seasonally. Persistent wheezing has been thought to be due to RSV and rhinovirus infection but the studies have shown that most of it disappears by 11 years of age.

The second type of wheeze, the multi-trigger wheeze is defined as by viral infections as well as by other triggers such as tobacco smoke and allergens. It is made clear that use of persistent wheeze causes confusion as the term is based on the long term outcome. History is primarily useful to diagnose the preschool wheezing when the child is not having wheeze during consultation. Identification of wheeze from history may be difficult. This term is used by parents and healthcare workers to describe different respiratory disorders. Children with doctor diagnosed wheeze has shown greater airway resistance than when the wheezing history was given by the parents.[42]

As per GINA guidelines 2015, wheezing may be interpreted differently by different observers (parent /carer versus the health care provider), the time of reporting? (Retrospectively versus in real time), the area from where it is reported?, (Developed countries versus countries with parasites) and the cultural importance given to that symptom in that area.

In asthma cough is non–productive recurrent and or persistent. It is associated with intermittent wheezing and difficulty in breathing. The other diseases associated with cough are common cold and upper respiratory tract diseases.

Breathlessness: Different terms may be used by the caretakers, such as 'difficult breathing', 'heavy breathing', 'shortness of breath'. In infants and toddlers crying and laughing are equivalent to exercise.

Activity and social behaviour: Physical activity can lead to wheezing, cough in young children. Therefore these children abstain from strenuous play or exercise. Hence history of daily activities of child should be taken. Tiredness or mood changes reported by parents may indicate uncontrolled wheezing.

3.2.2 Tests to diagnose wheezing in preschool children

There is no standardized test to diagnose asthma in children 5 years and younger.

Following things can help in diagnosis of recurrent wheezing in children.

Therapeutic trial: A trial of treatment from as needed short acting beta agonist (SABA) and regular low dose inhaled corticosteroids (ICS) may help to differentiate asthma form other respiratory diseases.

Tests of atopy: Skin prick testing or allergen specific immunoglobulin E can be used to assess the sensitization to allergens. In infants skin prick testing is not a reliable test for confirmation of atopy. Usually atopy is demonstrated by children over three years.

Chest x-ray: To exclude structural anomalies, chronic infections, foreign body it is useful.

Lung function testing: As children below five years are unable to perform spirometry because it requires forceful expiration. If forceful mannouvres are performed they lack in repeatability. The bronchial provocation test cannot be performed in small children. At four to five years spirometry by experienced technician can be performed with visual incentives.

Exhaled nitric oxide: In children which present with recurrent cough or recurrent wheezing fractional concentration of exhaled nitric oxide (FeNO) can be measured. If FeNO is elevated > 4 weeks it may indicate the diagnosis of asthma.

Risk profiles: To identify the wheezing children who are less than five years various risk profile tools have been prepared. The Asthma Predictive Index (API) this is useful in studying children who have four to five wheezing episodes in a year. In a study by Brand et al[42],

it was shown that children with positive API have a 4-10times greater risk of developing asthma between ages 6-13 years.

The children less than five years need further investigations if there is failure to thrive, clubbing, persistent vomiting with respiratory symptoms, neonatal or very early onset of symptoms, continuous wheezing, wheezing not controlled by controller asthma treatment, symptoms not associated with typical triggers such as environmental tobacco smoke, focal lung signs or cardiovascular problem and disproportionate hypoxia.[43]

3.2.3 Prevention of wheezing episodes and asthma in young children

GINA guidelines 2018 has gone further in wheezing in children who are less than five years and indicate that the asthma or wheezing is secondary to interaction between gene and environment. A‘window of opportunity’ is present in utero and early life to prevent development of wheezing episodes and asthma. Certain environmental factors have been proposed such as nutrition, allergens and pollutants. The maternal diet and weight gain during pregnancy is studied. In a study decreased risk of asthma in the offspring was associated with the increased ingestion of peanut and milk during pregnancy. Obesity in mother and weight gain during pregnancy can lead to increased incidence of asthma in children. But at present no recommendation is made about food intake during pregnancy and weight gain during pregnancy.

Breast feeding has been recommended for asthma prevention but no consistent evidence exists to support this. Breast feeding can decrease wheezing episodes in childhood but was not able to prevent development of asthma.

Vitamin D intake in mother was supposed to decrease the risk of wheezing illness in child. But randomized control trials of vitamin D supplementation in pregnancy did not prove it.

Delayed introduction of solids have been recommended by many pediatirc agencies and societies to prevent allergies. At present guidelines do not recommend avoidance of foods giving rise to allergy to prevent wheezing episodes.

Meta-analysis has not provided any evidence for use of Probiotics for prevention of allergic diseases.

Exposure to indoor allergens such as dust mite is more linearly correlated with development of asthma. The association of pet allergen is linked with risk of asthma according to some studies but can give rise to decreased risk of allergy in other studies. Dampness, visible mold in the home can lead to development of wheezing episodes. Multifaceted interventions in birth cohort studies showed it resulted in lower risk of asthma. These studies include Isle of Wight study, the Canadian asthma primary prevention study. However exact advice regarding exposure of allergen during pregnancy is not yet possible.

Maternal smoking during pregnancy was associated with effect on young children. Exposure to outdoor pollutants is correlated with increased risk of asthma.

Hygiene hypothesis suggests that early contact with micro-biota is useful in prevention of asthma. Children staying on farms and those consuming raw milk have less chances of developing wheezing episodes. The children exposed to endotoxin in bedroom have less risk of developing wheezing.

Vaginal delivery leads to exposure of a newborn to the mother's vaginal micro flora which may be beneficial for the baby. The children born by caesarian section have more chances of developing asthma.

Use of antibiotic during pregnancy and after delivery in infants and children may give rise to increased risk of asthma later in life. Analgesics such as paracetamol may be associated with asthma. Vaccinations in children do not increase the risk of wheezing. Psychosocial factors may influence the child to develop wheezing. Premature babies may develop recurrent wheezing due to infection by respiratory syncytial virus. This can be prevented by injections of palivizumab (monoclonal antibody against respiratory syncytial virus).[44]

The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study in the United Kingdom looked at maternal reports at birth to six months and 36 months to 42 months early onset wheeze was defined as between birth and six months and late onset wheeze between 36 to 42 months. Those who wheeze at both times were labeled as persistent wheezers.

The study showed 59% had infrequent wheeze, transient wheeze in 16%, prolonged early wheeze in 9%, intermediate onset

wheeze in 3%, late onset wheeze in 6% and persistent wheeze in 7%.[45]

Savenije et al[46] compared phenotypes of asthma in ALSPAC and PIAMA study and came to the conclusion that the phenotypes in both studies are comparable and environmental and genetic studies may be helpful in finding origins of asthma.

In MAS (multizentrische Allergistudie) and PASTURE (Protection against Allergy: Study in Rural Environment) trial the phenotypes identified were benign, symptomatic and severe. It was found that the poly sensitization of allergens is more likely to result in asthma than mono sensitization. The severe class was associated with higher IgE production and decreased lung function.[47]

Mechanisms of development of allergy cohort (MeDALL), had similar findings that poly sensitization rather than mono sensitization leads to severe asthma and allergic symptoms.[48]

In the Canadian asthma primary prevention study (CAPPS) a cohort of 546 children was followed who were related with asthma patients from birth to 15 years. The early life interventions were done. These interventions involved avoidance of house dust mite, environmental tobacco smoke, pet allergens and promotion of breast feeding and use of partially hydrolyzed formula. Three wheezing phenotypes were identified low progressive, early transient and early persistent. The interventions decreased the probability of asthma at school age only in early persistent group.[49]

Urban environment and childhood asthma (URECA) study: In this study five different phenotypes were identified. They were low

wheeze/low atopy, low wheeze/high atopy, transient wheeze/low atopy, high wheeze/low atopy, high wheeze/high atopy. 442 children in inner city were followed from birth to seven years. High wheeze/high atopy and high wheeze /low atopy groups were found to have more possibility of asthma and they were not exposed to indoor allergens. Prenatal smoke exposure was associated with high wheezing and low atopy group and maternal stress had the same effect.[50]

In a study by Depner et al[51] comparing clinical and epidemiologic phenotypes on a birth cohort, it was found that clinical phenotypes were well supported by latent class analysis, thus children with clinically conspicuous but undiagnosed disease were identified. Recurrent unremitting wheeze emerged as alternative asthma definition for epidemiologic studies. The phenotypes identified were asthma diagnosis, Multi-trigger wheeze, unremitting wheeze, recurrent unremitting wheeze, frequent wheeze and episodic wheeze. Recurrent unremitting wheeze was the most specific and unremitting wheeze at least once emerged as the most sensitive definition of asthma.

Asthma risk factors: Genetic factors, perinatal exposures and interactions between genetic factors and perinatal factors give rise to development of wheezing episode. Some of these clinical indicators of risk are used to predict which children will develop wheezing in older childhood.

Atopy: Predisposition to allergy was found to be the risk factor in Tucson study. Higher proportion of allergic sensitization at six years was seen in late onset and persistent wheezing phenotype. In Avon

study iso-allergic sensitization was more in intermediate onset wheezing, late onset wheezing and persistent wheeze. They had clinician diagnosed asthma at 7.5 years of age.

Non-atopic wheeze usually present in first year of life. In patients with non atopic wheeze, wheezing episode decrease with increasing age. They usually wheeze with only viral infections.

In children with atopic wheeze, wheezing starts after one year of age and persists into adolescent age. Risk factors usually found are history of asthma in parents, male sex, atopic dermatitis, eosinophilia and development of wheezing during lower respiratory tract infections.[1]The other risk factors found are early sensitization to food allergens and sensitization to multiple allergens. If symptoms are present in between the wheezing episodes it also suggests likelihood of development of asthma.

Lung function: It has been documented that lung function is reduced in patients with persistent wheezing. Children who had normal function at one year had decreased function at six year of age.[1, 52-55]

Respiratory pathogens such as viral illnesses have been studied in cohort study from birth to six years of age and in a study by Jackson et al[56] it was found that rhinovirus illness was most associated with development of asthma risk at the age of six years. Asthma risk was also observed after RSV infection. The odds ratio for rhinovirus was 9.8 and for RSV it was 2.6.[55]

Microbial imbalance: It was seen that infants treated for bronchiolitis with azithromycin developed less incidence of

wheezing in the next year as compared to those who were not treated. The investigators attributed this to role of azithromycin as anti-inflammatory or modification of airway microbiome.[56]

Vitamin D: Protection from asthma in children was found in mothers with good vitamin D intake. It was postulated that vitamin D helps in development of lung in utero.[57]

Asthma predictive index: It was designed as part of Tucson study. The stringent criteria is defined as wheezing in first three years of life, one of the two major criteria(MD asthma or MD eczema i.e. doctor diagnosed asthma or eczema) and two of the three minor criteria (MD allergic rhinitis, recurrent wheezing and eosinophilia >4%). The loose criteria was wheezing before three years and one of the major criteria or two of the three minor criteria. The parameters were chosen from univariate analysis.[1]

Need for the diagnosis of wheezing in children

3.3.1 Change in epidemiology

Acute respiratory infections (ARI) lead to maximum morbidity and deaths in children in children below five years of age. They account for 20% of child deaths per year. Acute respiratory tract infections (ARI) are usually thought of as pneumonia but actually ARI denotes many respiratory diseases.

The world health organization has taken initiative to decrease mortality and morbidity of pneumonia by integrated management of childhood Illness (IMCI) guidelines. This involves simple clinical signs and optimal antibiotic treatment.[59]

Deaths due to pneumonia have declined at slower rate since 2000.The reasons for this slow decline have not been evaluated clearly. Several studies have brought into notice that the guidelines recommended by IMCI if used in practice can lead to increased diagnosis of bacterial pneumonia and increased use of antibiotics.[60]

Studies from Asia report that a many children who did not respond to of antibiotic treatment for pneumonia had wheeze.[61, 62] WHO has recommended a trial of bronchodilator in children with wheeze and fast breathing before making a diagnosis of pneumonia.[62] The symptoms and signs of asthma in young children are similar to lower airway infections, such as bronchitis, bronchiolitis, and pneumonia.[63] Infants with viral bronchiolitis do not respond to bronchodilators. Hence children with wheeze should be managed with different management protocol.

Pneumonia is described as an acute infection of alveolar tissue of lung. It is caused by bacteria, viruses or other microorganisms. a a chest x-ray is supposed to be the gold standard in the diagnosis of bacterial pneumonia. The WHO IMCI strategy gave a classification of pneumonia for children in resource limited setting which excluded fever to increase sensitivity. But this strategy decrease specificity. The diagnosis of pneumonia was made by clinical findings.

The definition of Asthma is inflammatory disorder with variable airway obstruction. There is recent increase in incidence of wheezing episodes in children. The wheezing episodes are exacerbated by viral infections. These episodes usually start early in

childhood. In a study it was observed that in non-severe bacterial pneumonia diagnosed by fast breathing, chest x-ray showed finding suggestive of consolidation in less than 20% children.[64]

In microbiological studies it was observed that viruses were predominant pathogens.[62]

The ISAAC study demonstrated that there is high prevalence of asthma in school children in low income countries. The prevalence of asthma was 13.3% in 6-7 year old children in Mozambique.[63] Prevalence in Bangladesh was 16.1%. In Tanzania the prevalence of wheezing in children was 14%. In Brazil prevalence of wheezing in children was 12.5%.

3.3.2 Early diagnosis of wheezing episodes

The majority of later diagnosed cases of asthma begin before 3 years of age. Up to 80% of cases of asthma are diagnosed before the age of six years. Early symptoms are correlated with increased severity of the disease and bronchial hyper responsiveness.[65,66] Definitions given by Tucson study about early wheezing, non-atopic wheezing and late onset wheezing are too simplistic. These phenotypes actually depend on disease severity and can change over time.

No specific cause for asthma has been identified but various environmental and genetic factors are responsible for development of asthma. The factors proposed in the development of asthma or multi trigger wheezing in children are viral infections, prematurity, exposure to tobacco smoke, exposure to increased levels of air

pollution, atopy, family history of eczema or asthma, or blood eosinophilia.[67]

Half of the children with wheezing improve when they reach school age.[68] However in atopic and more severe cases persistence of wheezing is possible. The remission in asthma symptoms is less likely in severe patients. Currently there is no objective measure of measuring severity of the wheezing episode. Hence there is need to develop objective method of measuring the severity of bronchial hyper responsiveness and as well as frequency of number of episode.

Development of wheezing can cause poor quality of life in patients as well as in their caretakers if not properly treated.[68] The important question is which child is going to develop asthma? It is still not answered properly. GINA guidelines 2014 acknowledged that asthma can develop in preschool children. Asthma like symptoms are the frequent causes of visit to emergency.

3.4 Issues in the management of wheezing in children

3.4.1 Differential diagnosis of wheezing in children

Wheezing is common in children less than five years. Wheezing is associated with large proportion of childhood respiratory infections. WHO has developed the algorithm for control of ARI in view of more cases of pneumonia to decrease the mortality. In the last few decades there is concern about the identification and treatment of respiratory problems in children below five years. The diagnosis of wheeze depends only on giving

nebulization and observing the child. There is no clear algorithm for such children or follow up in WHO strategy.[69]

The different entities causing wheezing in children below five years are bronchial asthma, bronchiolitis and pneumonia. The rare causes are inhaled foreign bodies, compression of airways from outside by lymph nodes or tumour and vey rarely pulmonary edema.

Wheezing is very common symptom in children below five years. Children with wheeze may have fast breathing and /or chest in drawing. Therefore they may be categorized as pneumonia or severe pneumonia. Thus using WHO/IMCI algorithm leads to over diagnosis of pneumonia. In various studies performed in India and outside it was seen that asthma was diagnosis in fifty percent of the cases and pneumonia in one third cases. The incidence of wheezing was found to be 22% to 75%. The incidence of wheezing was higher in children presenting with in drawing. Thus fast breathing and chest in drawing can be suggestive of wheezing and not only pneumonia.

The diagnosis of wheeze in community depends on giving three cycles of inhaled bronchodilators at 15 minutes interval to children with audible wheeze, fast breathing and /or lower chest in drawing. Audible wheeze is the criteria to make a diagnosis of wheeze in the field. It has been found that audible wheeze is found in only 29.3% of children when compared to and auscultable wheeze.[70, 71]

3.4.2 Lack of clarity in diagnosis

The present strategy of depending on audible wheeze leads to underutilization of bronchodilators and increased treatment with

antibiotics. Hence different strategies have been tried. It was seen that asthma related wheeze could be predicted by history of two or more previous episodes (sensitivity 84%, specificity 84%).If fever is used as criteria (sensitivity 73% and specificity 84%).[72] This algorithm helps in restricting unnecessary prescription of antibiotics and underutilization of bronchodilators.

The other option tried was to give trial with inhaled bronchodilators in children with fast breathing to exclude diagnosis of pneumonia. It was found that the respiratory rate decreased below age appropriate cut offs in 46-62% children.[73]

Change in the indrawing was in children was somewhat less. But this approach resulted in considerable overuse of bronchodilator. Hence diagnosis by a skilled healthcare worker using stethoscope should be done.

The WHO strategy was formulated towards treatment of pneumonia. As the epidemiology has changed and prevalence of wheezy episodes has increased there is need to accurately diagnose and give appropriate bronchodilator therapy.

Viruses cause of wheezing in most cases. The viruses associated are RSV, rhinovirus adenovirus and human boca virus. Most literature suggests viruses causing wheezing. There is some evidence suggestive of bacterial infection causing wheeze.[73] Viral and bacterial co-infection is also a common finding.[73]

The further progress of children treated with inhaled bronchodilator therapy only once is not very clear. Thus follow up of these children should be there. Hence operational research should

be done as a field trial to test the feasibility and usefulness of treatment of wheeze by trained health staff.[66]

Major changes in understanding about childhood asthma have been seen in definition, environmental factors, natural progress of the disease, triggers and treatments. The prospective field studies have shown that asthma starts in early childhood. Recent evidence has shown that asthma is not a low prevalence disease in young children in developing countries. The ISAAC study demonstrated a significant prevalence of asthma in school children in countries with low income. In Mozambique it was 13.3%, in Bangladesh it was 16.1%.[63] In South Africa a delay in the diagnosis of three years was observed in many children who were letter diagnosed as asthma.[74]

Amirav et al[75] reviewed the respiratory rate as diagnostic tool for pneumonia. In various studies it was observed that the counting of respiratory rate was faulty by community health worker. They observed that while counting respiratory rate manually, breaths were difficult to observe continuously. It is a difficult procedure and a device would be appropriate for the proper count.

3.5 Impulse oscillometry

3.5.1 Assessment of lung function

There are different methods to assess lung function in children. The different methods are spirometry, FeNO, lung volumes X-ray, CT images of the lung. Impulse oscillometry is one such technique useful for assessment of lung function in children. The reason is it is simple to use even in children 3 to 6 years of age where spirometry cannot be utilized easily. It does not require any forceful manouvre by the patient hence minimal cooperation is

required from the patient. The changes in lung function are assessed by putting a sound wave in the airway hence the stimulus can be modified from outside without asking the patient to do any particular manouvre.

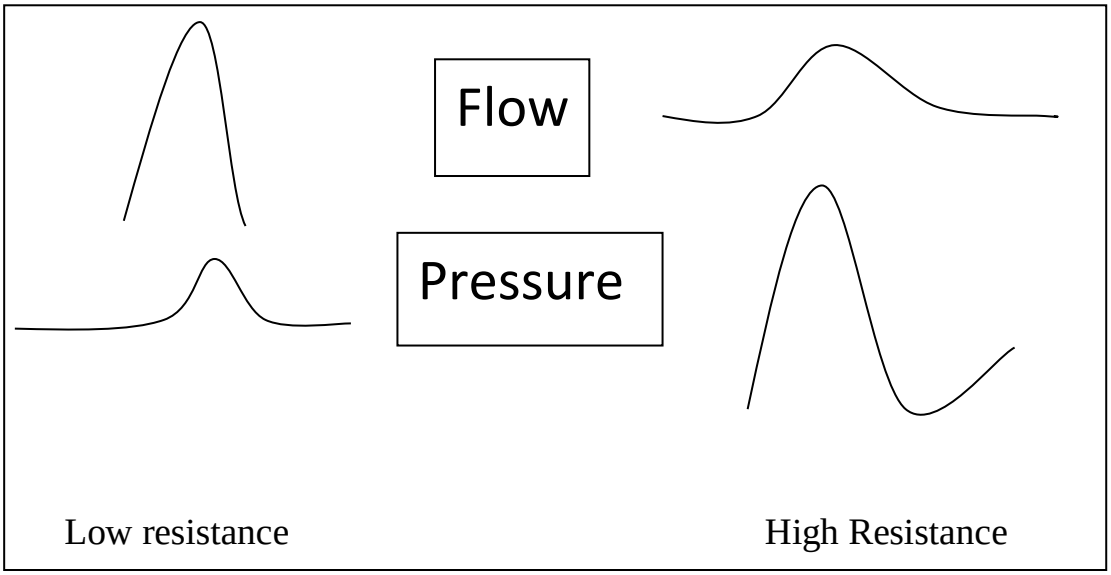


Figure 3.5.1: The relationship between pressure, flow and resistance. (Akio NIMI presentation WAO international Scientific Conference (WISC) 2014

In spirometry what we measure is flow and volume and from that inference about resistance is drawn. (Figure 3.5.1) Sometimes the forceful mannouvres in spirometry alter the resistance in airway.

3.5.2 Principles of impulse oscillometry

In impulse oscillometry the resistance is measured by sending a pressure wave applied externally and measuring the respiratory airflow. External pressure wave generator produces artificial impulse-shaped test signals of multifrequency. The pneumotachograph and transducer measure airway opening pressure and airflow to calculate respiratory impedence (Zrs) (figure 3.5.2).

$Zrs = P/V$ Equation: 3.1

$= R$ (resistance) $+ X$ (reactance)

Mathematical manipulation (i.e. Fourier transformation) enables measurement of resistance (R) and reactance(X) at each frequency. [76]

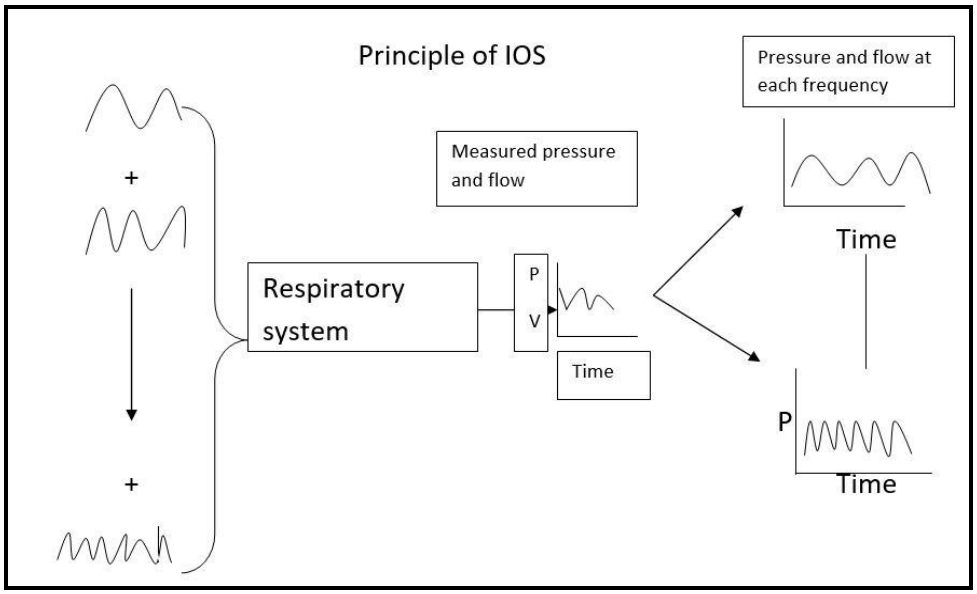


Figure 3.5.2: Principle of Impulse oscillometry system (Akio NIMI presentation WAO international Scientific Conference (WISC) 2014)

Resistance: The resistance in impulse oscillometry is denoted by Rrs. Normally there is some difference in R5 and R20 in children that is total and central resistance. It decreases with age. In small airway disease the resistance at lower frequency such as R at 5Hz is high. Thus R at 5Hz is much higher than R at 20 Hz. In large airway or upper airway obstruction the R at 5Hz and R at 20 Hz both are increased.

Lung reactance: Reactance is how the alveoli, diaphragm, chest wall, all react to the pressure wave. It actually indicates how much these structures are expandable. Low reactance means the structures have little stretch and recoil of lungs. It decreases in idiopathic fibrosis of the lung.

3.5.3 Studies of impulse oscillometry system in children for assessment of bronchodilation

Hellincks et al[77] examined 281 children age 2.7-6.6 years. All the children were subjected to impulse oscillometry then 200 ug of salbutamol was given by inhaler with spacer. The Rrs 5 of non-asthmatic children correlated with height. The change in Rrs at 5 Hz was significant after inhalation of salbutamol. (0.09±0.25) In placebo group it was 0.004±0.14. The difference in change of Rrs5 in asthmatic and non-asthmatic was not very significant. Hence they suggested a cut off of -40% to diagnose asthma. The asthmatics in this study were stable and half of them were being treated. Also the severity of asthma was not taken into account. Most of them were with mild asthma.

Delacourt et al[78] measured impulse oscillometry parameters in 313 patients with suggestive history of asthma, cough at night and allergic rhinitis. The age group was 3years to 15 years. 181 children also performed forced expiratory manouvre with spirometry. They concluded that FOT can be used to assess reversible broncho constriction in children.

Malmberg L P et al[79] studied 109 children age group 2 to 7 years. Children underwent impulse oscillometry and it was repeated after 300 micrograms of salbutamol inhalation in 89 children In 19 children placebo was given as inhalation. Zrs and Rrs 5-20 showed negative correlation with age, height and weight. Xrs 5-20 showed positive correlation with age height and weight. Height after logarithmic conversion came out as best independent variable. After

inhalation of placebo the oscillometric variable did not change significantly. The salbutamol group had, the mean (SD) change in Rrs5 was -0.187kPa $l^{-1}s^{-1}$. Both within test and between test repeatabilities for the measurement of respiratory resistance was acceptable. Thus usefulness of forced oscillation technique was shown in examining respiratory function and bronchial lability in preschool children.

Marotta et al[3] showed that impulse oscillometry can be used to measure dysfunction of the lung in children with four years of age by comparing with spirometry. Children who had 2-3 episodes of wheezing before two years were enrolled for study. They were tested with impulse oscillometry before and after inhalation with bronchodilator, spirometry, allergy skin testing and parents were asked to fill a questionnaire B by American Thoracic society for asthma in childhood. A positive response to 4 out of 5 questions was taken as specific for physician diagnosed asthma and bronchial hyper responsiveness. It was observed that there were no significant differences in R at 5Hz and R at 10Hz (resistance) before bronchodilator response but significant difference was observed in children with asthma after bronchodilator response. The response to bronchodilator was more in atopic children. But spirometry did not show any significant difference in baseline or after broncho dilatation response in atopic and non-atopic asthmatic patients. They concluded that preschool children with asthma and atopy are associated more with development of persistent asthma. IOS can be used by clinicians to identify these patients in which medical and

environmental intervention may improve their condition. Bronchodilator response 20-25% at 5 Hz was found significant.

Olaguibel et al[80] studied 33 children with asthma three to six years old. All the children underwent IOS measurement (R5rs, R20rs, and X5rs) three times initially, after placebo and salbutamol inhalation. Spirometry (FEV1) and body plethysmography (sRaw) were also done at the beginning, after placebo and salbutamol. Baseline within test coefficient of variation (CV %) and between test repeatability (baseline-placebo) were measured. Bronchodilator response was evaluated by standard deviation index. Baseline repeatability for R5rs was 4.1%. It decreased by 2 SD after bronchodilator inhalation. It correlated with FEV1 (baseline r = 0.51 and after bronchodilation r = 0.63) and sRaw (baseline 0.49) and post salbutamol (r=0.54). Change in the IOS values and sRaw was seen. Thus they concluded that IOS parameters in young asthmatic are reproducible and sensitive. (R5rs) were reproducible and were correlating with parameters of spirometry and plethysmography.

Amra et al[81] published the reference values for impulse oscillometry. They examined 509 children. They came out with reference equations for R at 5 Hz, R at15 Hz, R at 25 Hz and X at 5Hz, X at 15 Hz and X at 25 Hz. Age and height were found to be significant independent variables affecting the resistance.

Komarow et al[4] evaluated the impulse oscillometry for bronchodilator response in 117 children to distinguish asthmatics from non-asthmatics. It showed statistically highly significant response. Spirometry done in 66 asthmatic children and 16 non

asthmatics FEV1 did not show any significant difference in these two groups. Thus they concluded that IOS is a noninvasive approach in diagnosis and treatment of lung diseases in children and should be considered as adjunct or alternative to spirometry.

Mochizuki et al[82] in their review stated that forced oscillation technique is very easy to perform in children and more than 80% children are able to perform it in first attempt. It can be used to assess real time narrowing of airway in asthmatic and non-asthmatic children and R at 5Hz was reproducible.

Saadeh et al[83] evaluated 39 children with asthma and used impulse oscillometry for initial diagnosis and follow up. They evaluated these children for short acting bronchodilator response with impulse oscillometry and spirometry at base line and after 3 months of inhaled corticosteroid treatment. IOS showed improvement in function both initially and after long term corticosteroid use. Thus they found that IOS can be used for diagnosis and follow up of asthma in children without the extra efforts required for spirometry.

Kalliola et al[84] studied 121 children aged 3.7 to 8.1 years. 31 children were with probable asthma, 61children with history of wheezing disorder at an early age and 15 children were with bronchopulmonary dysplasia. 14 children were healthy children were enrolled as control group. Indirect airway hyper responsiveness (AHR) was assessed by two parameters exercise and mannitol challenge tests. Direct AHR was assessed by methacholine challenge using Impulse oscillometry. AHR to exercise was measured as increase in R at 5Hz by at least 40%. Dose causing an

increase in R at 5Hz was calculated for mannitol and methacholine. AHR with exercise was found to differentiate children with lung symptoms. AHR to methacholine was useful in differentiating healthy children from children with lung symptoms, early wheezing disorder and bronchopulmonary dysplasia. Mannitol test was not able to differentiate between the study groups. They concluded that methacholine and exercise challenge tests with IOS can differentiate children with suspected asthma and may help practically.

Due to these research papers an attempt was made by other authors to develop reference values in children for impulse oscillometry.

3.5.4 Studies about impulse oscillometry reference values

Asumpcao et al[85] studied 864 children who were 6 years to 14 years in age from Brazil and finalized 123 children for measurement. Impulse oscillometry was carried out in all the children as per ATS criteria. Spirometry was also performed. Height, age and weight were recorded. IOS values as per age were finalized for R5, R10, R20, X5, X10, X20 and resonance frequency and AX. Regression equations were derived. Height was found to affect most of the values of IOS.

Reference values for impulse oscillometry were developed by Gochicoa-Rangel et al[86] in healthy Mexican children and adolescents. In 283 healthy children with average age of 8.3 years they measured the various parameters given by impulse oscillometry. The median Zrs 5 was 0.72, Zrs 20 was 0.47, Rrs5 was 0.67, Rrs20 was 0.47 and difference between Rrs 5-Rrs 20 was 0.19.

The Xrs5 was -0.23, Xrs 20 was 00, Fres was 21.67 and AX was 1.70. Normal distribution was not observed in most of the IOS variables.. The variables skewed to right were (Zrs, Rrs and AX) and variable which skewed to left was (Xrs). Age, height and weight were found to be correlated to IOS in bivariate analysis. The values fit in straight line when log 10 was used. All IOS values were analysed separately for gender. Multiple regression analysis showed height was the most important variable influencing IOS parameters. Age also had influence on the regression models. Body weight was excluded from all reference models.

Gochicoa-Rangel et al[87] also tried to validate the reference equations. Hence 4-15 years old healthy children from Mexico City were selected and IOS was performed on them. The functional IOS parameters obtained were compared to 12 reference equations which were previously determined by different study groups from different ethnic origin. The validation was done by analysis of the differences between measured and predicted values for each reference equation. The correlation and concordance coefficients adjustment by Z score values were also used for validation. Percentage of predicted value and the percentage of patients below the lower limit of normality or above the upper limit of normality were also calculated.

Duenas-Meza et al[88] measured impedence and bronchodilator response in children living at height of 2640 meter in 3 years to 5 years old living at high altitude to develop reference values for them. Ninety six children were examined and underwent IOS. Values for Rrs and Xrs at frequencies 5, 10, 15 and 20 Hz were measured. Height was found to be most important independent variable

influencing IOS parameters. Relative change of 28% to 36% after bronchodilator was considered higher range of normal.

3.5.5 Impulse oscillometry system and spirometry

Batmaz et al[89] examined 35 children with acute exacerbation, 107 stable asthmatic and 103 healthy children with IOS and spirometry before and after use of salbutamol for bronchodilatation and found that parameters of impulse oscillometry correlated with parameters of spirometry. The age group was 6 years to 17 years. Spirometric reversibility was observed with $\Delta R5 < -22.34$ and ΔAX -39.5.The criteria developed by Neve for spirometry in children less than five years was used to compare with impulse oscillometry parameters. T These were found in 85%, 93%, 94%, 90%, and 89% of children. They suggested to choose the same threshold for all repeatability criteria, i.e., ΔFVC, ΔFEV_1, and $\Delta FEV_{0.5} \leq 110$ ml and $\leq 10\%$. In conclusion, a majority of patients with asthma were able to perform at least two acceptable maneuvers. Spirometry therefore can be used to assess respiratory function in preschool children with asthma.

Jorge et al[90] reviewed 81 publications regarding impulse oscillometry and asthma. They found 63 matching with their criteria. They noted that IOS measured the mechanical properties of lung and spirometry measures the flow of air. They observed that there is correlation in parameters of spirometry and impulse oscillometry and impulse oscillometry is more sensitive in diagnosis of asthma than spirometry and in follow up studies also it detects the airway obstruction earlier than asthma.

Knihtila[91] demonstrated that impulse oscillometry in preschool years was correlated with spirometry in adolescent age group. The Rrs5 and frequency dependent resistance were measured in preschool children and reassessed with spirometry in adolescent life. They studied 154 asthmatic children. The odds ratio for Rrs5 was 5.9 and for dRrs /df was 8.2. Thus in children who develop asthma, IOS done in preschool age is associated with spirometric lung function at adolescence.

Thus the impulse oscillometry is useful in refining the diagnosis of obstructive airway diseases, it can measure the quantity of airway obstruction and the reversibility of airway obstruction and thus help in proper therapy and helps in monitoring of the disease.

3.5.6 Sensitivity of impulse oscillometry in young asthmatics:

Klug et al[92] showed by measuring resistance pre and post bronchodilator response by interruptor technique, impulse oscillometry and plethysmography that sensitivity of clinical assessment of respiratory function in young children is poor. Lung function measurements are therefore useful in these children for assessment of clinical condition as well as for monitoring treatment response.

Delacourt et al[93] tried to compare the impulse oscillometry and interruptor technique to assess the obstructive airway disease in preschool children. As interruptor technique can also be used in preschool children to assess lung function. They concluded that the impulse oscillometry was better correlated with spirometry than interruptor technique.

Konstantinou et al[94] studied the airflow limitation in preschool children. They followed 93 children for two years. 43 children developed virus induced wheeze in two years. The change in R5 values before and after bronchodilation -20.5% had a sensitivity of 70% and specificity of 76%. This longitudinal study clearly showed the usefulness of impulse oscillometry to assess lung function in preschool children.

CHAPTER-IV
PULMONARY FUNCTION TESTS

4.1 History of pulmonary function testing and spirometry

4.2 Tidal breathing measurement

4.3 Thoraco-abdominal motion analysis

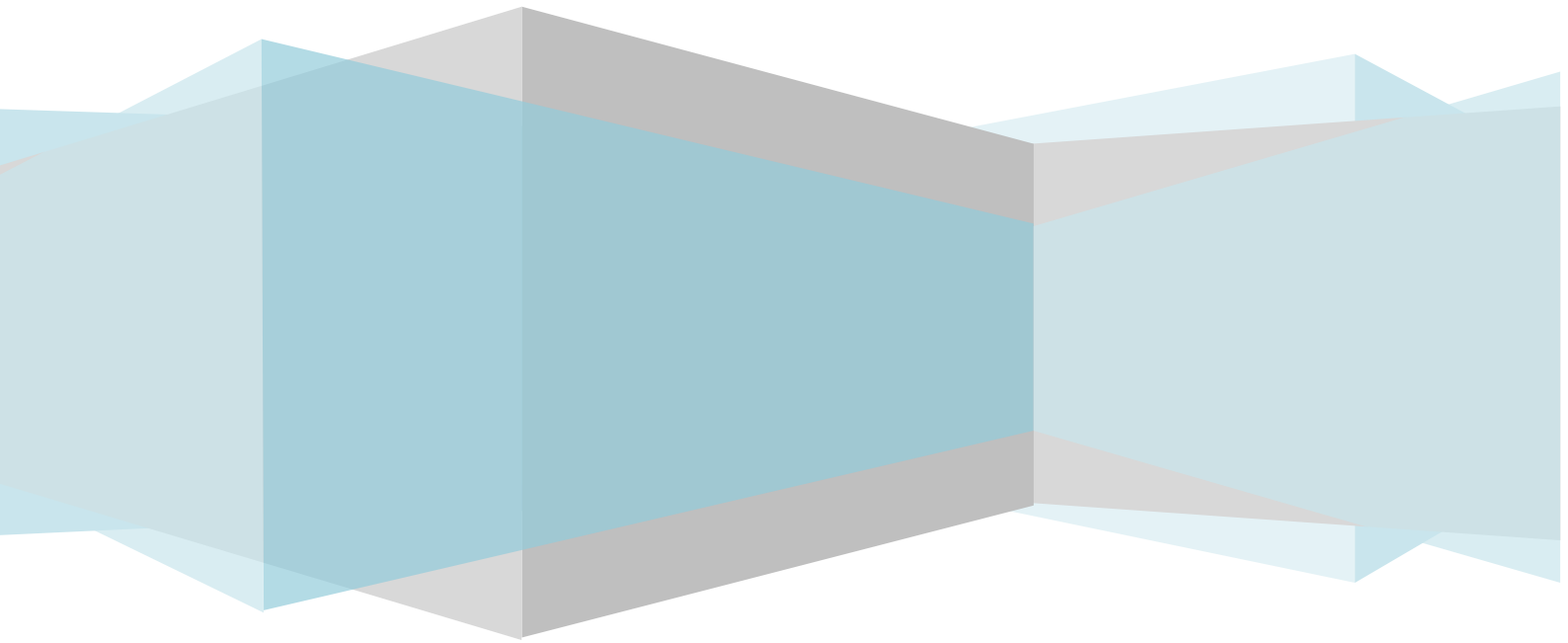
4.4 Interruptor technique

4.5 The forced oscillation technique

4.6 Multiple breathe inert gas washout technique

4.7 Body plethysmography

4.8 Exhaled nitric oxide



PULMONARY FUNCTION TEST

4.1 History of pulmonary function testing and spirometry

Gibson et al[95] in his review of history of spirometry enumerated that earliest measurement of lung volumes was done by mathematician Giovanni Alfonso Borelli (1681). He estimated with a cylindrical glass tube, in this liquid was sucked. The bore of the tube and the height of the meniscus were used to measure the volume. The measurements were inaccurate as there were pressure changes in the tube.

Estimate of vital capacity was made by Stephan Hales (1727). He measured it with forcefully expiring in a bladder. The estimate of vital capacity was made by displacement of water by Archimedes principle.

Something close to spirometer was built by William Clayfield (1800). It was called mercurial air holder.

Boerhaave measured the inspiratory capacity by putting the person in water tub and measuring rise in water level after inspiration. Edward Kentish (1814) designed a pulmometer by putting graduated bell over water and introducing air from above.

John Hutchinson carried out vital capacity measurements in 4000 person. He showed that it gives the diagnosis of tuberculosis much earlier than by stethoscope. He modified the water filled spirometer and made it utilizable in day to day practice.

In 1925 a detailed report was published by Myers of the conditions in which vital capacity is reduced. In 1933 Hammansen developed the concept of maximum voluntary ventilation. This was being used for assessment of the patient before surgery.

After nebulization with adrenaline the expiratory volumes increase in asthma was shown by Barach in 1938. The studies done by Coumand and Richards and Baldwin and others lead to the classification of respiratory diseases into obstructive and restrictive.

The FEV1 was described separately by Tiffeneau and Pinelli in Paris (1947) and Gaensler in the USA (1951). It was shown by Gaensler that maximum breathing capacity correlated with FEV1 rather than at 2 second or 3 second capacities. FEV1 became a regular measurement from that time.

Maximum flow volume curves were prepared in 1960. It gave a good visual perception of inspiratory and expiratory flow. Maximum mid expiratory flow rate actually MMEF 25-75 became available before FEV1 as it does not require fast responding instrument. It can decrease in restrictive conditions and it has a wide range. FEV6 has been added as a new parameter so as to make patients with prolonged respiration more comfortable.

In current situation FVC and VC are same in healthy subjects but FVC is less in patients with airway diseases. An obstructive airway disease can be defined as decrease in the ratio of FEV1 to FVC or FEV1 to VC. Diagnosis of restrictive disease is made by reduced FEV1 and VC and a normal ratio. Ideally it is measured by measurement of lung volume (by inert gas dilution technique or by

body plethysmography). Spirometry has helped to diagnose obstructive airway disease in children above six years. The graphical representation is easy to interpret and helpful in diagnosis, assessing severity of the disease and even prognosis of the patient. Various studies have demonstrated use of spirometry in follow up of patient. Weight, height, age, sex, environmental factors, ethnicity, prematurity, patient cooperation and efforts and technical factors influence spirometry parameters. It is difficult to use in children. With the development of incentive and modified criteria spirometry may be performed more easily in children.

Airway resistance was measured by plethysmography by measuring airflow and driving pressure and calculating R_{aw} (airway resistance), sR_{aw} (specific airway resistance) and sG_{aw} (specific airway conductance).[96]

The other tests which can be performed in children are tidal breathing measurements, interrupter technique, forced oscillation technique and multiple inert gas washout technique.

4.2 Tidal breathing measurement

Tidal expiratory flow is measured in tidal breathing measurement and analysis of thoraco-abdominal motion is also done. Flow signals are measured at upper airway (with mask/mouthpiece and pneumotachometer) and volume signals are measured at the chest wall (with ribcage and abdominal bands). $t_{PTEF}/t_{E\ and}$ $V_{ptef}/V_{E.,\ the}$ these are two expiratory measurements used to analyze tidal breathing. Most of the studies are done in infants.[6]

4.3 Thoraco-abdominal motion analysis (TAA)

The children with respiratory diseases have indrawing, which indicates a significant respiratory disease. To measure the magnitude of chest indrawing thoraco-abdominal motion wall analysis is used. Normally rib cage moves outward during inspiration and abdomen also moves outward. With increase work of breathing rib cage does not move with abdominal movement as intrathoracic pressure is negative and it may move inward in severe cases. Thoraco-abdominal motion analysis measures the abnormal chest and abdominal wall excursion. Thus TAA is increased in increased respiratory resistance due to upper and lower airway diseases, in parenchymal diseases with reduced lung compliance and in diseases with increase chest wall compliance such as neuromuscular diseases.[6]

4.4 Interrupter technique

In interrupter technique, the airflow is suddenly obstructed at the mouth due to this obstruction the pressure in mouth and pressure in alveolus becomes equal. Rint is defined as equilibrated pressure divided by the airflow measured immediately before interruption. Reference values are available for interrupter technique.[6]

4.5 The forced oscillation technique

The FOT is simple, non-invasive technique performed during tidal breathing. A pressure wave generated by external source is given to the airway at the mouth. The relationship between pressure and flow is analyzed to find out impedence of the respiratory

system. The resistance to flow is sum of frictional losses due to airway and compliance and inertia due to lung tissue. It requires minimum cooperation from the children and it is non invasive technique. The measurement therefore can be performed in children who are above the age of three years in pulmonary laboratory, hospital and in school.

Impulse oscillometry system consists of sinusoidal sound wave generated by loudspeaker passed in airway of the patient via a pneumotachometer connected to a mouth piece. A bias tube is attached from loudspeaker to pneumotachometer. A pneumotachometer is a device used to measure airflow quantitatively (Figure 4.1)

The principle is lower frequencies penetrate the lung till the periphery and higher frequencies reach only up to the beginning of the lower airway (Figure 4.2)

In a normal lung the R at 5 Hz is equal in all lower and higher frequencies. (Figures 4.3 and 4.4)

If there is peripheral obstruction the R at 5 Hz is increased and R at 20 Hz is not elevated. (Figures 4.5 and 4.6)

In lung mechanics, pressure generated by respiratory muscles (trans-pulmonary pressure) is related to tidal volume and flow. When pressure difference is divided by flow it gives value of resistance. (kPa $.L^{-1}s^{-1}$) and dividing the pressure difference by change in volume gives value of elastance ($kPa.L^{-1}$) the reciprocal of compliance.

Lung resistance indicates the frictional losses in the airways and the lung parenchyma. The reactance is proportional to elastance. FOT uses an external pressure or flow fluctuation is used in forced oscillation technique and the mechanical response is measured according to pressure and flow.

The total impedence is called Zrs. The in phase component of Zrs is called as Rrs. The out of phase component of resistance is called as reactance and labeled as Xrs.

Rrs is the measured airway resistance. (Change in pressure as to change in flow)

Xrs denotes the elasticity (It is the relationship between change in pressure and change in volume) and inertive properties (it is the change in pressure and volume acceleration).

Rrs and Xrs are expressed as function of oscillation frequency (f) .Thus R5 Hz is resistance at 5 Hz frequency.

The elastic properties are more visible at lower frequencies and the inertia is more important at higher frequencies.

In obstructive diseases the Rrs is higher and is negatively frequency dependent. It means at higher frequency Rrs is lower.

In obstructive disease the Xrs is lower and increases with increasing frequency. It means at higher frequency Xrs is higher.

Usually multiple frequency device is preferred as compared to single frequency.

Pneumotachometer: Along a tube of constant resistance difference in pressure between the two ends is proportional to airflow. This is the principle of pneumotachograph. It is a short lightweight tube with two side openings and it is used to monitor the pressure difference across a heated mesh, which is used to maintain laminar airflow. In this way it measures airflow.

Transducer is a device to produce electrical signals from another form of energy such as pressure. Pressure transducer converts pressure into electrical signal and measures pressure.

Multiple frequencies generated by loudspeaker are sent to mouth. Usually these frequencies range from 4 to 30 Hz.

The oscillatory signal is applied at the airway opening where flow and pressure are measured. The same can e obtained by variation in pressure over the chest and volume measured at the mouth. In this way artifacts due to upper airway are decreased.

Zrs is the relationship between trans -respiratory pressure and the airway flow. The computer is used to generate signal which is given by a loudspeaker to the patient through a pneumotachometer and bacterial filter which is connected to the mouthpiece. Loudspeaker and pneumotachometer are connected by bias tube. The dead space in the instrument is formed by mouthpiece, bacterial filter and flow meter. It amount to a volume of 50-70 ml. Subject's head can be put in a chamber to minimize the upper airway wall shunting.

Transducer specifications: The pressure transducers should be low in sensitivity to accelerations. They should be protected from vibrations. The flow meter and the pressure transducer should be linear (within 2%) up to at least 1 $L.s^{-1}$ up to 0.5 kPa, respectively.[96]

The impulse oscillometry system should measure a load of <0.1 kPa. s. L-1 below 5 Hz. When using composite signals, the loudspeaker should be able to develop a peak-to peak pressure variation of 0.2 kPa at the airway opening. The upper limit of the pressure in the system in the system should not be more than 0.5kPa.[6]

4.6 Multiple –breathe inert gas washout technique

Multiple –breath inert gas wash out technique is used to calculate ventilation distribution throughout the lungs and to calculate the FRC. It is easy to perform in any age group the cooperation required is minimal. The lung clearance index (LCI) is measured by cumulative expired volume required to remove an inert gas from the lungs which is divided by FRC. It detects airway damage and helps in monitoring of course of the disease. It has been used in cystic fibrosis in children. It can be performed even in small children as it does not require cooperation and it is performed during tidal breathing. The inert gases used are nitrogen (N_2), argon, helium and sulfur hexafluoride.[6]

4.7 Body plethysmography

Airway resistance is measured by calculating air flow and pressure by body plethysmography. In this lung is considered as

tube attached to a flexible parenchymal compartment. The pressure required to move air in and out is

P= EV+RV'+IV" Equation 4.7.1

P=pressure, V=volume, R=resistance, V'=flow, V"= acceleration and E=elastance, R=resistance, I=inertance.

If volume fluctuations are less, the EV becomes zero. If breathing frequency is less IV" would be negligible. Thus P = RV'. Thus if pressure at the alveolus and flow is known resistance can be calculated. At condition of no flow mouth pressure is equal to alveolar pressure. Thus after sudden interruption mouth pressure is measured. The resistance is called $R_{aw.}$ The corrected resistance is measured for lung volumes and is called sR_{aw} or $sG_{aw.}$[97]

4.8 Exhaled nitric oxide

Increased levels of fractional exhaled nitric oxide indicate eosinophilic airway inflammation in airways. It can be performed even in preschool children. Measurement of nasal FeNO is useful in primary ciliary dyskinesia. Standard equipment measures at flow of 50 ml/s ($FeNO_{50}$) Alveolar NO (CA_{NO}) requires measurement at 100 to 300 ml per second flow. Nitric oxide when measured at higher flow reflects alveolar rather than central airway NO.[6]

PULMONARY FUNCTION TEST PHOTOGRAPHS

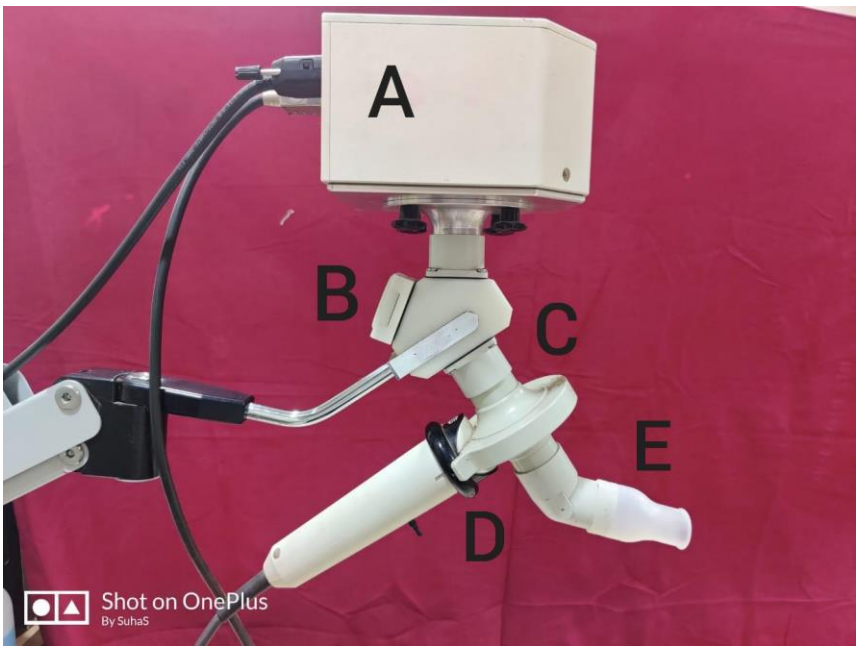


Figure 4.1: Impulse oscillometry (IOS) machine

A: Loudspeaker or external pressure wave generator

B: Resistor

C: Pneumotachometer

D: Transducer and

E: Mouth piece

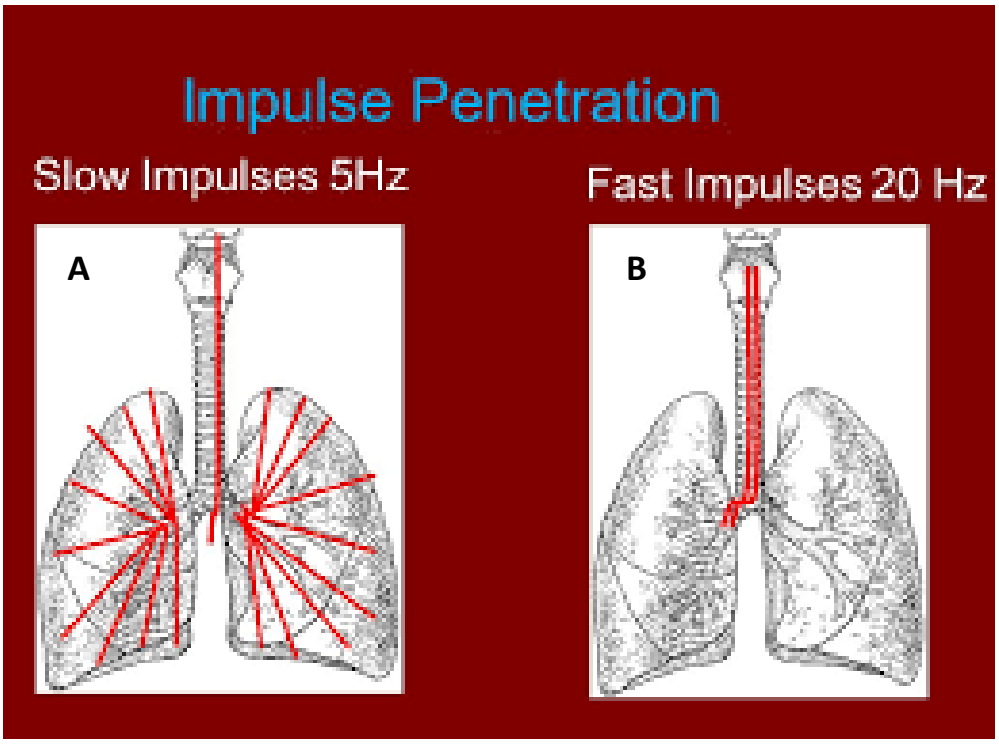


Figure 4.2: Penetration of frequency

(Impulse oscillometry By Dr/ Hossam EL-din mohamed Lecturer of chest diseases Ain Shams university)

A: 5 Hz impulses travel to the end

B: 20 Hz impulses travel till initial portion

DR. SUHAS KULKARNI

CareFusion

Identification: 163

Last Name:
Date of Birth: 06/04/2015
Sex: female

First Name:
Age: 3 Years
Height: 92 cm
Weight: 11.9 kg

Impuls-Oszillometrie

		Pred	Act1	%(A1/P
Date			10/10/	
Time			15:50:	
VT	[L]		0.24	
AX	[kPa/L]		5.53	
Z at 5 Hz	[kPa/(L/s)]	1.36	1.38	101.5
R at 5 Hz	[kPa/(L/s)]	1.29	1.31	101.4
R at 10 Hz	[kPa/(L/s)]	1.19	1.00	84.0
R at 15 Hz	[kPa/(L/s)]	1.12	0.94	83.5
R at 20 Hz	[kPa/(L/s)]	1.07	0.85	79.8
X at 5 Hz	[kPa/(L/s)]	-0.41	-0.44	107.3
X at 10 Hz	[kPa/(L/s)]	-0.15	-0.32	217.1
X at 15 Hz	[kPa/(L/s)]	-0.16	-0.26	163.5
X at 20 Hz	[kPa/(L/s)]	0.02	-0.20	-912.7
Resonant frequency	[1/s]		29.85	
VEX max	[L]			
AX at VEX	[kPa/L]			

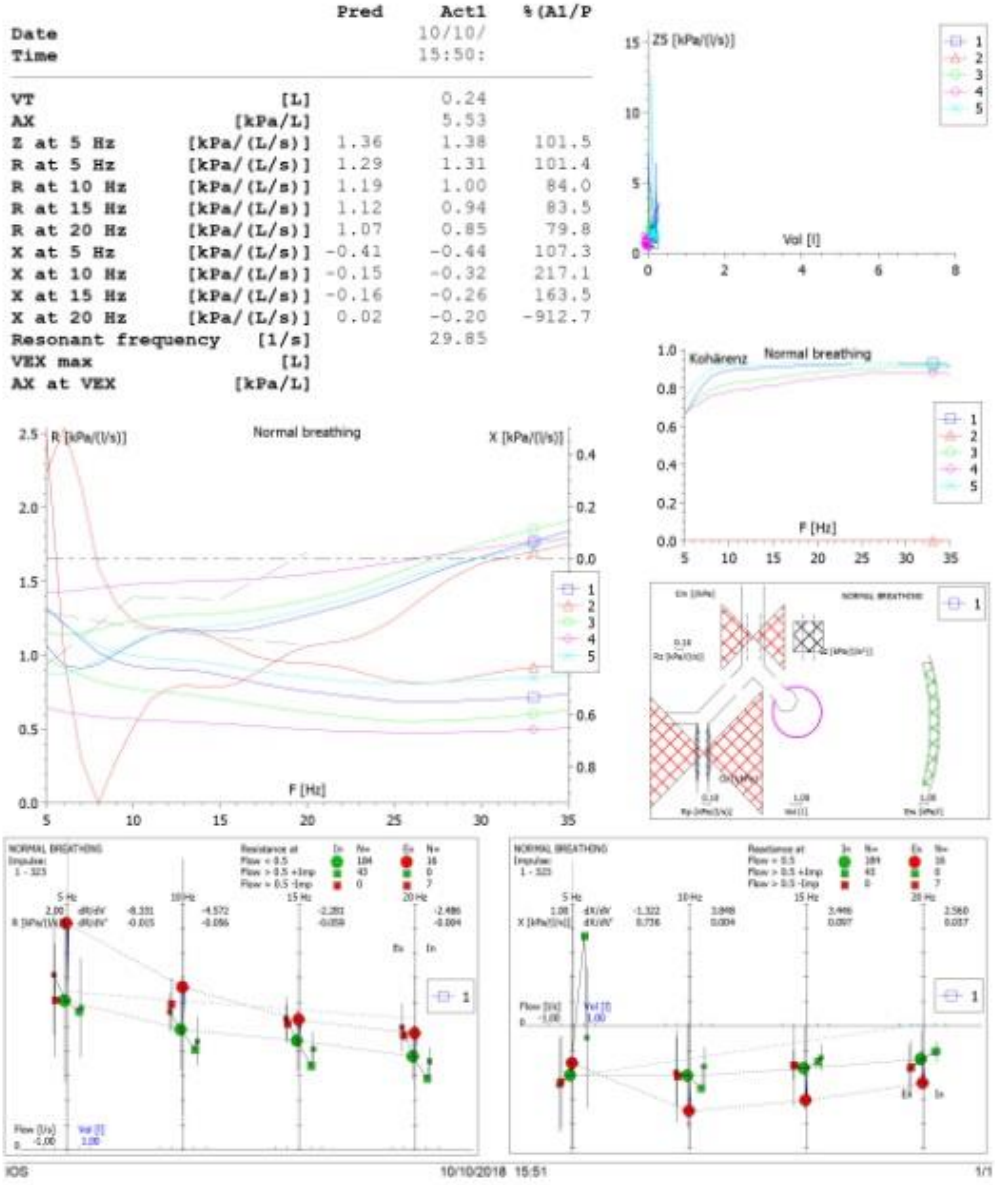


Figure 4.3: Normal graph – No airway obstruction

DR. SUHAS KULKARNI

CareFusion

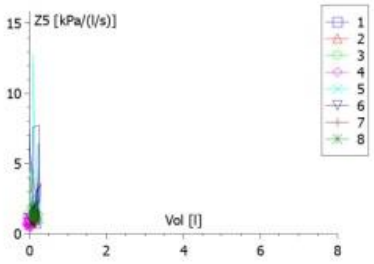
Identification: 163

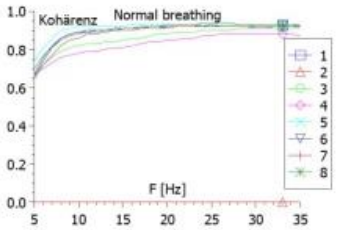
Last Name:
Date of Birth: 06/04/2015
Sex: female

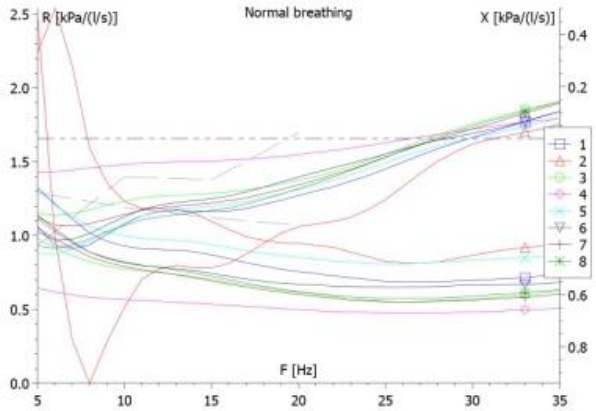
First Name:
Age: 3 Years
Height: 92 cm
Weight: 11.9 kg

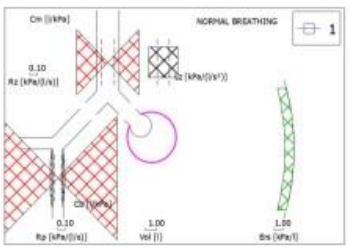
Impuls-Oszillometrie

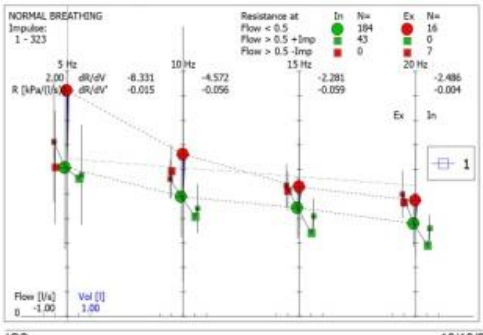
		Pred	Act1	%(A1/P
Date			10/10/	
Time			16:37:	
VT	[L]		0.22	
AX	[kPa/L]		5.43	
Z at 5 Hz	[kPa/(L/s)]	1.36	1.19	87.4
R at 5 Hz	[kPa/(L/s)]	1.29	1.11	86.3
R at 10 Hz	[kPa/(L/s)]	1.19	0.82	69.0
R at 15 Hz	[kPa/(L/s)]	1.12	0.72	64.5
R at 20 Hz	[kPa/(L/s)]	1.07	0.62	58.1
X at 5 Hz	[kPa/(L/s)]	-0.41	-0.41	100.6
X at 10 Hz	[kPa/(L/s)]	-0.15	-0.33	224.2
X at 15 Hz	[kPa/(L/s)]	-0.16	-0.28	173.5
X at 20 Hz	[kPa/(L/s)]	0.02	-0.19	-898.7
Resonant frequency	[1/s]		27.84	
VEX max	[L]			
AX at VEX	[kPa/L]			











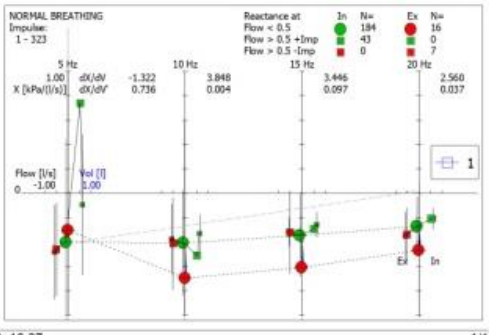


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Figure 4.4 No significant change in R at 5Hz after bronchodilation

DR. SUHAS KULKARNI

CareFusion

Identification: 159

Last Name:
Date of Birth: 23/08/2013
Sex: female

First Name:
Age: 5 Years
Height: 106 cm
Weight: 15 kg

Impuls-Oszillometrie

		Pred	Act1	%(A1/P
Date			05/10/	
Time			16:44:	
VT	[L]	0.24	0.26	107.8
AX	[kPa/L]		12.99	
Z at 5 Hz	[kPa/(L/s)]	1.01	2.00	196.9
R at 5 Hz	[kPa/(L/s)]	0.96	1.90	197.7
R at 10 Hz	[kPa/(L/s)]	0.86	1.14	132.7
R at 15 Hz	[kPa/(L/s)]	0.83	0.91	109.8
R at 20 Hz	[kPa/(L/s)]	0.79	0.75	94.6
X at 5 Hz	[kPa/(L/s)]	-0.31	-0.60	193.4
X at 10 Hz	[kPa/(L/s)]	-0.11	-0.71	662.1
X at 15 Hz	[kPa/(L/s)]	-0.13	-0.60	468.0
X at 20 Hz	[kPa/(L/s)]	0.05	-0.45	-969.5
Resonant frequency	[1/s]		35.53	
VEX max	[L]			
AX at VEX	[kPa/L]			

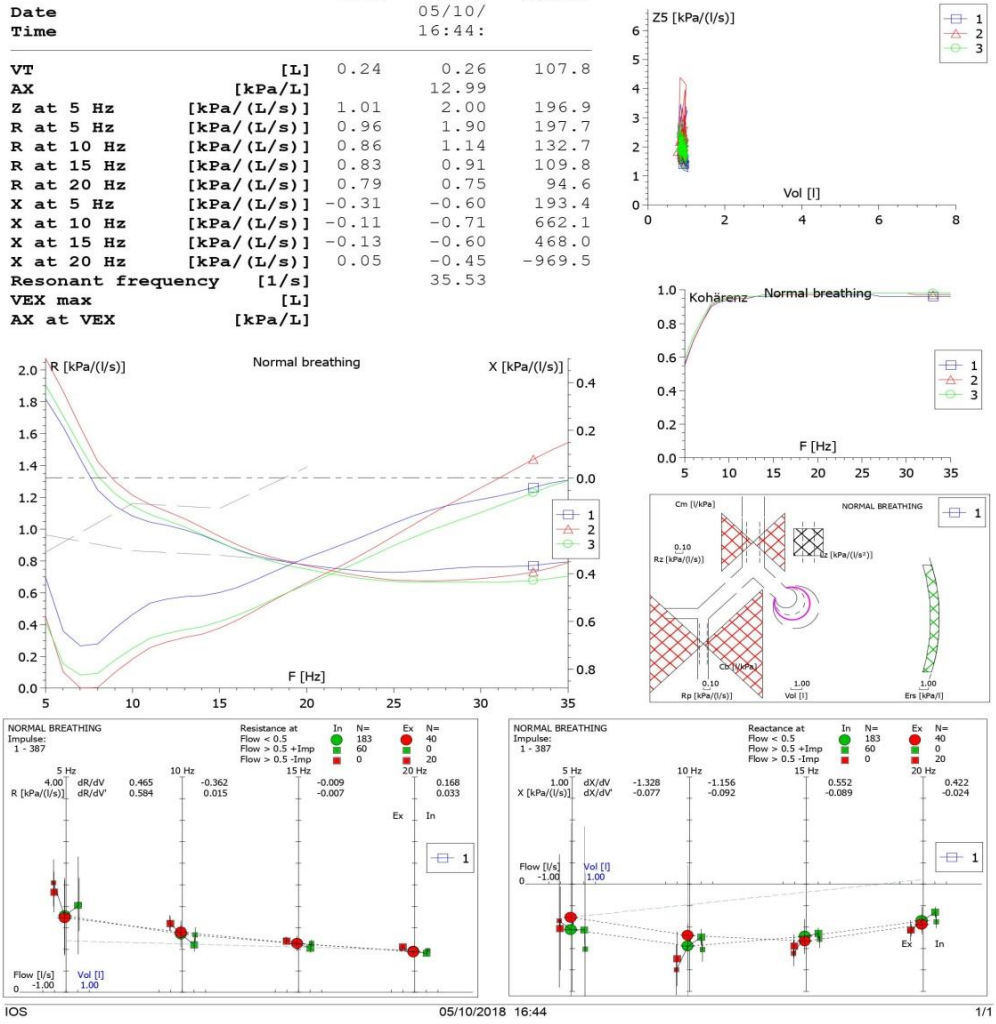

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Figure 4.5: Peripheral airway obstruction

DR. SUHAS KULKARNI

CareFusion

Identification: 159

Last Name:
Date of Birth: 23/08/2013
Sex: female

First Name:
Age: 5 Years
Height: 106 cm
Weight: 15 kg

Impuls-Oszillometrie

		Pred	Act1	%(A1/P
Date			05/10/	
Time			17:13:	
VT	[L]	0.24	0.26	109.5
AX	[kPa/L]		2.16	
Z at 5 Hz	[kPa/(L/s)]	1.01	1.03	101.8
R at 5 Hz	[kPa/(L/s)]	0.96	1.02	105.8
R at 10 Hz	[kPa/(L/s)]	0.86	0.81	94.5
R at 15 Hz	[kPa/(L/s)]	0.83	0.77	92.9
R at 20 Hz	[kPa/(L/s)]	0.79	0.75	94.7
X at 5 Hz	[kPa/(L/s)]	-0.31	-0.17	53.4
X at 10 Hz	[kPa/(L/s)]	-0.11	-0.17	154.6
X at 15 Hz	[kPa/(L/s)]	-0.13	-0.11	86.8
X at 20 Hz	[kPa/(L/s)]	0.05	-0.05	-100.1
Resonant frequency	[1/s]		24.81	
VEX max	[L]			
AX at VEX	[kPa/L]			

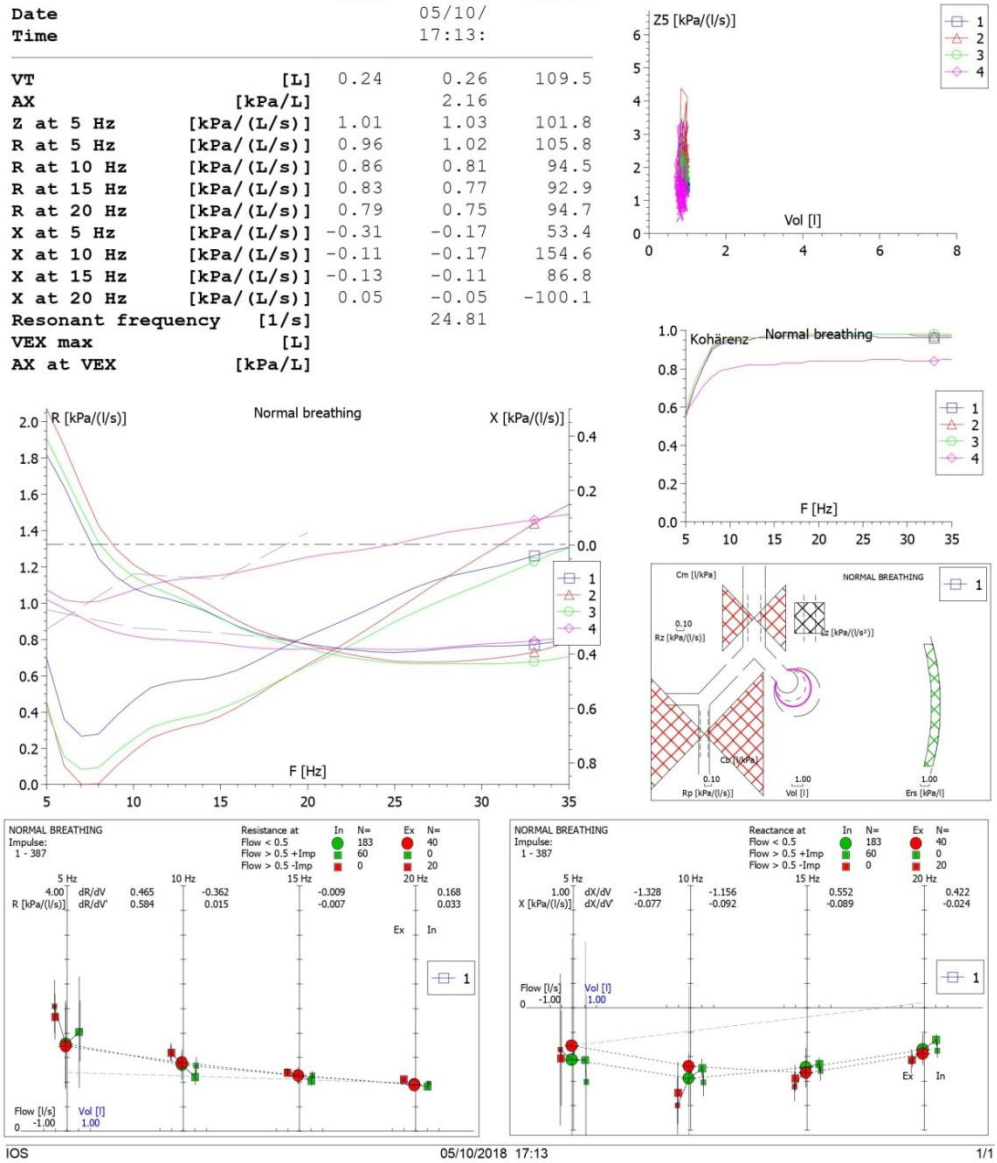

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Figure 4.6: After bronchodilation the R at 5 Hz is decreased > 25%.

CHAPTER-V
MATERIALS AND METHODS

5.1Ethics

5.2 Study design

5.3 Inclusion criteria

5.4 Exclusion criteria

5.5 Study duration

5.6 Methodology

5.6.1 Study design

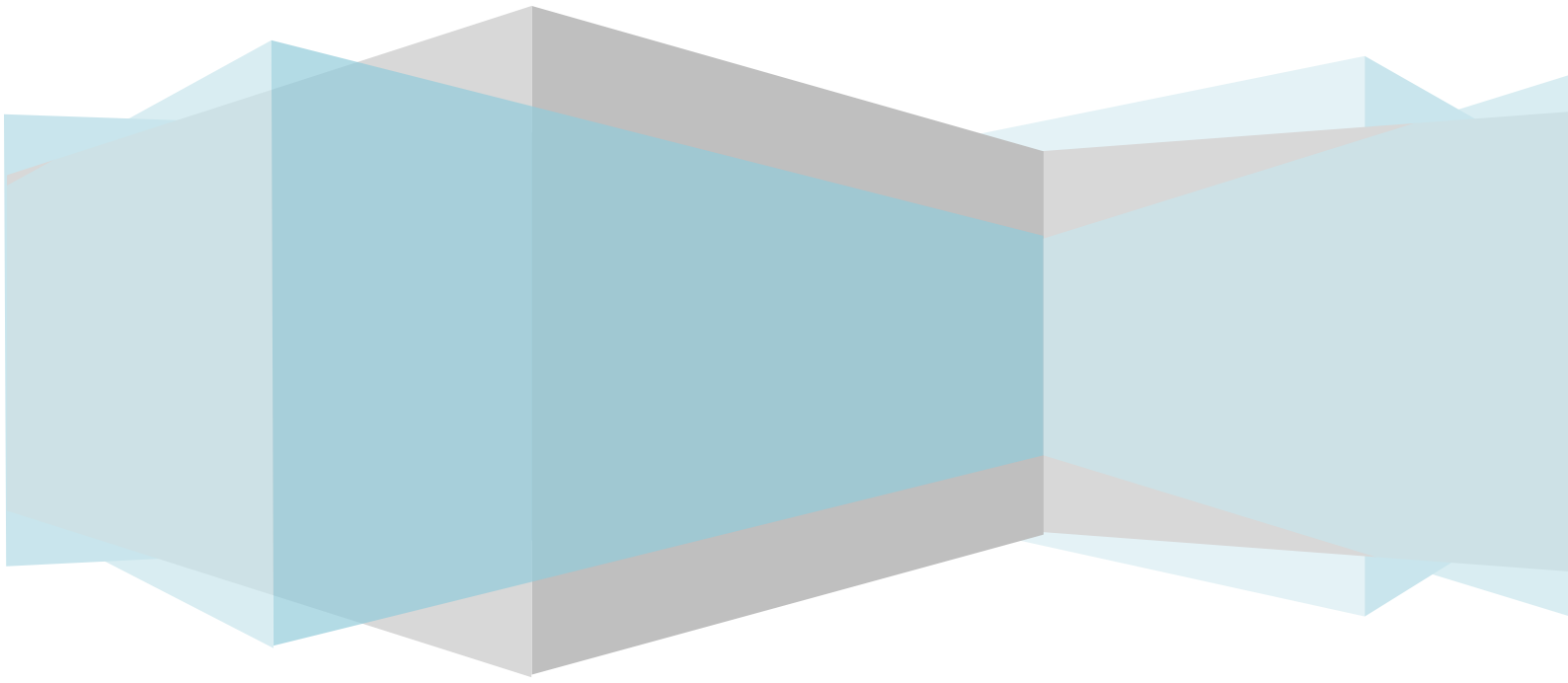
5.6.2 Sample size calculation

5.6.3 Study procedure and data collection

5.6.4 Impulse oscillometry technique

5.6.5Quality control

5.7 Statistical analysis and development of scoring system



MATERIALS AND METHODS

5.1 Ethics:

The study was conducted after obtaining permission from institutional ethics committee. Written informed consent was obtained from parents or guardians of all cases. Assent was not taken as all children were below seven years.

5.2 Study design:

It was experimental study conducted in Department of Pediatrics, D. Y. Patil Medical College, Kolhapur. The study was conducted on children in age group of three to six years with history of fever, cough, cold and breathlessness to differentiate between pneumonia and wheezing episode with the history and clinical examination and impulse oscillometry.

5.3 Inclusion criteria

Three to six years old children with history of fever, cough, cold and/or breathlessness visiting the outpatient department of D. Y. Patil medical College, Kolhapur whose parents gave consent.

5.4 Exclusion criteria:

1: Children with heart disease

2: Children with pneumothorax, and empyema.

3: Children ventilated previously.

5.5 Study duration:

The study was conducted from December 2016 to December 2019.

5.6 Methodology:

5.6.1 Study design

An interventional study was undertaken in paediatrics department of a tertiary care hospital from December 2016 to December 2019. The study was approved by the Institutional Ethical Committee (2016/35/PA-F dated September 19, 2016). The purpose and details of methods used in the study were explained to all the parents. A written informed consent was obtained from parents prior to the study. A total of 106 children within 3-6 years of age with history of fever, cough, cold and/or breathlessness where the diagnosis and differentiation between wheezing episode and other respiratory disorders was not obvious based on history and clinical examination were included. Children with congenital heart disease, Children with pneumothorax, and empyema and children ventilated after birth were excluded.

5.6.2 Sample size calculation:

$$n = \frac{(Z_\alpha)^2\, p(1-p)}{(d)^2}$$ Equation: 5.1

Where Z_α is the critical value of the normal distribution at α (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), p is the expected prevalence and d is the precision.

p = 30% and d = 0.1

The minimum sample size for given study is 80.

Considering this, 106 patients were enrolled in the study.

5.6.3 Study procedure and data collection

A pre-designed validated data collection form was used to collect demographic and clinical data such as symptom, duration and severity, details of routine clinical examination (cold, cough, breathlessness, fever, heart rate, respiratory rate, respiratory system examination, and oxygen saturation) for provisional diagnosis. Symptoms such as fever, cough, cold and breathlessness were graded by accompanying parents on arbitrary scale of 1 to 4 (1 being absence of symptom and 4 being severe). A Masterscreen Impulse Oscillometry system (IOS) (Care fusion Germany 234 GmbH Hochberg) was used in addition to history and clinical examination to make the provisional diagnosis. The system was calibrated for body temperature and pressure. The system was calibrated by 3 litre syringe provided by manufacturer every day. All the patients underwent IOS using nose clips and parent or guardian was advised to gently hold the sides of patient's face. Respiratory system resistance (R), reactance (X), total resistance (Z) were determined at 5, 10 and 20 HZ thrice before and 20 minutes after nebulization (2.5mg Salbutamol). (before covid pandemic with due precautions). The resonance frequency (Frs) and area of reactance (AX) were also measured. Three readings were taken. The average reading was used for the study. Final diagnosis was done by following patient clinically for up to 7 days. Diagnosis of wheezing episode was made by increased respiratory rate, presence of bronchovesicular breathing

and rhonchi. Diagnosis of pneumonia was made by respiratory rate more than 40/min, presence of crepitations on auscultation and x-ray chest suggestive of pneumonia.

5.6.4 Impulse oscillometry Technique

Initially the children were allowed to breathe through appropriately sized mouth piece. The child was seated comfortably and his or her head was in slightly extended or neutral position. The mouthpiece was kept in mouth of the child and child was asked to make a seal around it. Then the child was asked to breathe by mouth. Then it was attached to the machine. A nose clip was worn. The child was instructed to breathe slowly in a normal way. The child was instructed to avoid putting his or her tongue in mouthpiece. The cheeks and floor of mouth of the child were supported by the parents or technician to minimize vibrations in the upper airway. The recording covered several breathing cycles lasting more than 8-16 seconds. The recording was done after a proper breathing pattern was seen on the graph. The coherence was observed in the graph provided by the machine and results with coherence above 0.8 were considered for the study.

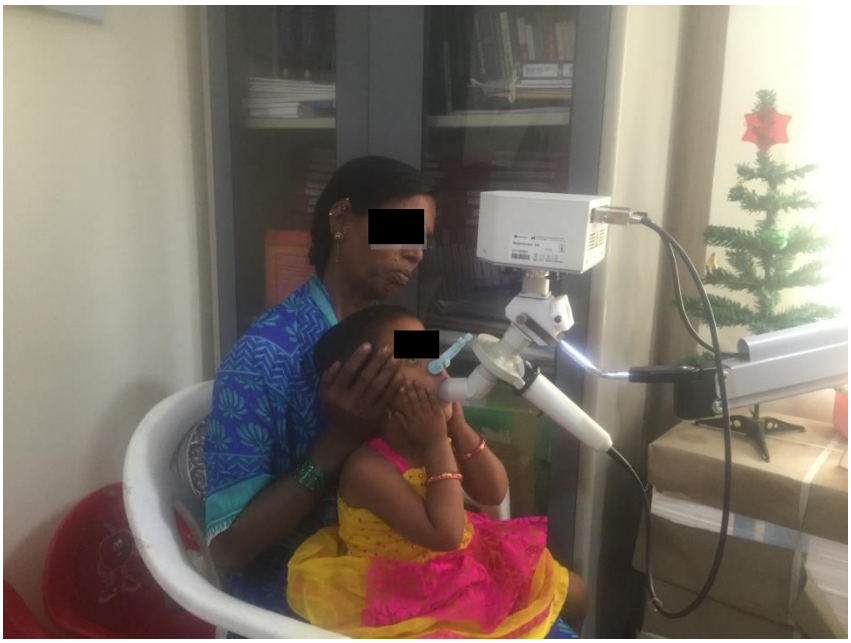


Figure 5.1: patient performing impulse oscillometry

5.6.5 Quality control :

Visual control: The actual display is seen while performing the test. The tidal breathing can be monitored visually by following the tracing so as to make out the artefacts. Mouth piece obstruction, closure of the glottis or swallowing was detected as decrease in the waveform or interruption of the waveform or as flat line on the tracing. Irregular breathing, rapid shallow breathing could be made out from the flow tracing. Leak around mouthpiece is suggested by sudden drop in the volume tracing.(figure:5.2)

All the examinations were carried out in child friendly environment by using toys and making it more like a play activity.

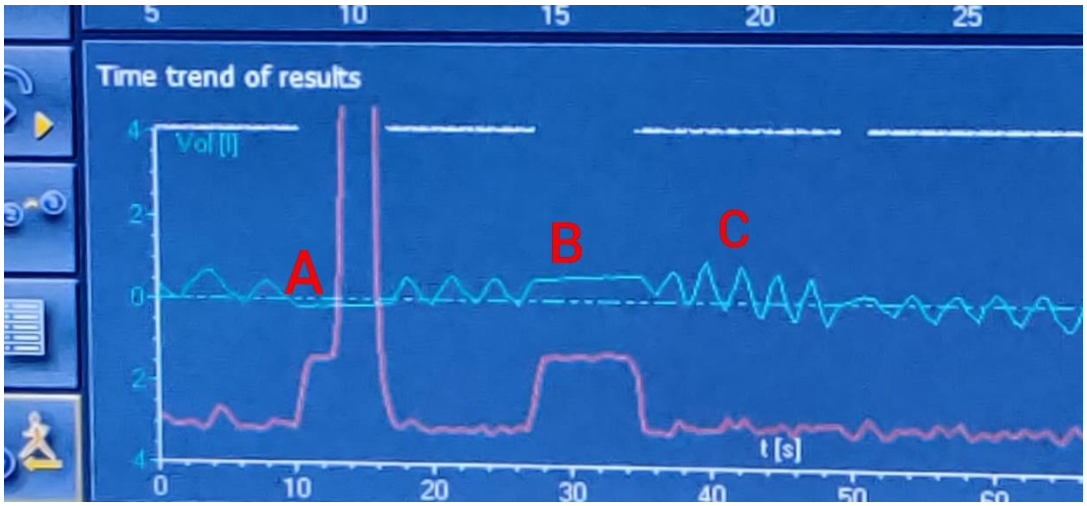


Figure 5.2 Artefacts during IOS

A: obstruction by tongue
B: Glottic Closure
C: Hyperventilation

5.6.7 Statistical analysis and development of scoring system

Collected data were analysed in R software (3.6.1). Paired T-test and Wilcoxon-Sign-Rank tests were used to find difference of respiratory resistance between pre and post IOS test. Mean values and 95% confidence intervals of the parameters were calculated as described by ATS guidelines. Correlation of height and R at 5 Hz was calculated to check uniformity of collected data and scatter plot was developed (ATS/ERS guidelines).[6] Logistic regression model was used to develop a scoring system to differentiate between wheezing episode and pneumonia. For diagnosis of wheezing episode cut-offs of the total scores, accuracy, sensitivity and specificity were calculated.

CHAPTER-VI
RESULTS AND DISCUSSION

6.1 Introduction

6.2 Frequency distribution of age

6.3 Frequency distribution of sex

6.4 Frequency distribution of weight

6.5 Frequency distribution of height

6.6 Frequency distribution of cough

6.7 Frequency distribution of cold

6.8 Frequency distribution of fever

6.9 Frequency distribution of breathlessness

6.10 Respiratory rate and heart rate

6.11 Rhonchi and crepts and final diagnosis

6.12 X-ray diagnosis and final diagnosis

6.13 Demographic and symptom analysis and final diagnosis

6.14 Analysis of Impulse oscillometry parameters

6.15 Impulse oscillometry parameters and final diagnosis

6.16 Correlation of height and weight with R at 5 Hz

6.17 Logistic regression analysis for prediction of diagnosis

6.18 percentage change in R at 5 Hz and final diagnosis

6.19 Development of scoring system

RESULTS AND DISCUSSION

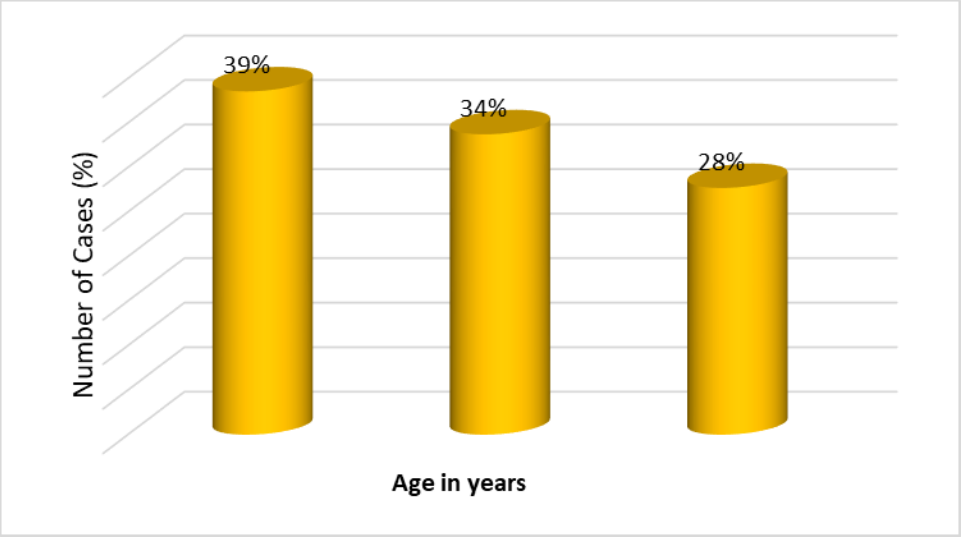
6.1 Introduction

The total children in the study were 106. Five children did not perform the impulse oscillometry properly hence they were excluded. Out of 101 patients 18 children were excluded as they did not complete the follow up. Hence analysis of 83 children was done.

6.2 Frequency distribution of age

Table 6.1: Frequency distribution of age. (n = 83)

Age	Frequency	%
3 to 4	32	39%
4 to 5	28	34%
5 to 6	23	28%



Graph 6.1: Frequency distribution of age in years.

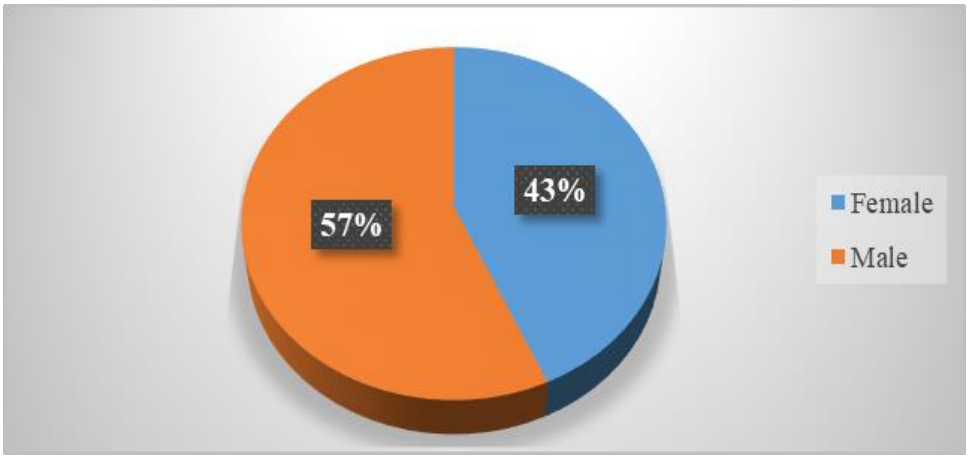
In the present study, most of the enrolled cases having age group is 3 years to 4 years (i.e., n = 32 (39%)), followed by age group 4 years to 5 years (n = 28 (34%)), then age group 5 years to 6 years (n = 23 (i.e., 28%)). (Table 6.1)

In our study, age distribution shows similar distribution of children in all age groups. The age group is similar to other studies done by Meza[88], konstantinou[94], Park, Olaguibel[80], Klug[92]. Others have used age group ranging from 3 years to 15 years in various studies. As spirometry can be performed in age group above 6 years, the impulse oscillometry system should be practiced in age group 3 years of age to 6 years of age.

6.3 Frequency distribution of sex

Table 6.2: Frequency distribution of sex.(n = 83)

Sex	Frequency	%
Female	36	43%
Male	47	57%



Pie chart 6.2: Frequency distribution of sex.

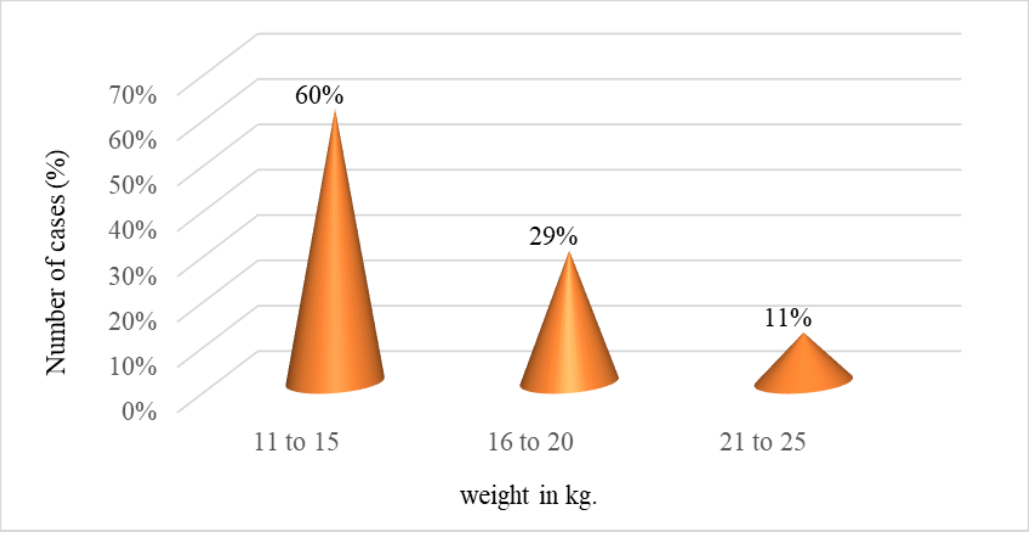
In the present study, there are 57% males and 43% females.

The sex distribution in our study was 57% male and 43% females (Table 6.2). This is similar to study by Konstnatinou[94] in which 54% males were present. In study by Komorrow at al[5] also the gender was equally represented in study cohort. Significant difference in the gender was not observed. Thus it indicates that wheezing episodes or pneumonia do not have much significant gender predilection.

6.4 **Frequency distribution of weight**

Table 6.3: Frequency distribution of weight.

Weight	Frequency	%
11 to 15	50	60%
16 to 20	24	29%
21 to 25	9	11%



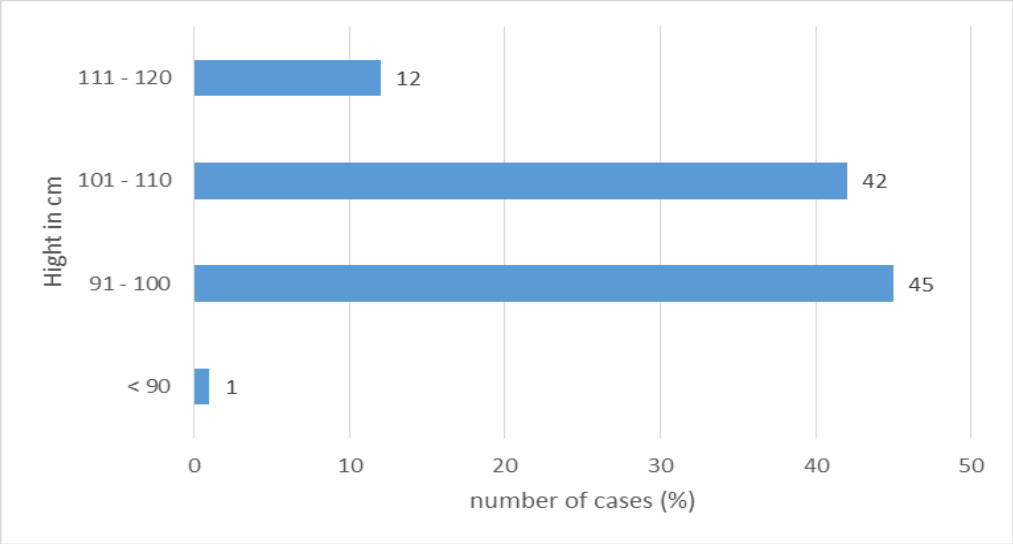
Graph 6.3: Frequency distribution of weight in kg.

In our study the weight of the participants varied from 11 kg to 25 kg. 60 % of the children were between weight 11 kg to 15 kg. (Table 6.3) The weight was negatively correlated with Resistance R at 5 Hz (correlation coefficient – 0.4738) (table 6.15)

6.5 Frequency distribution of height

Table 6.4: Frequency distribution of height.

Height	Frequency	%
< 90	1	1%
91 – 100	37	45%
101 – 110	35	42%
111 – 120	10	12%



Graph 6.4: Frequency distribution of height.

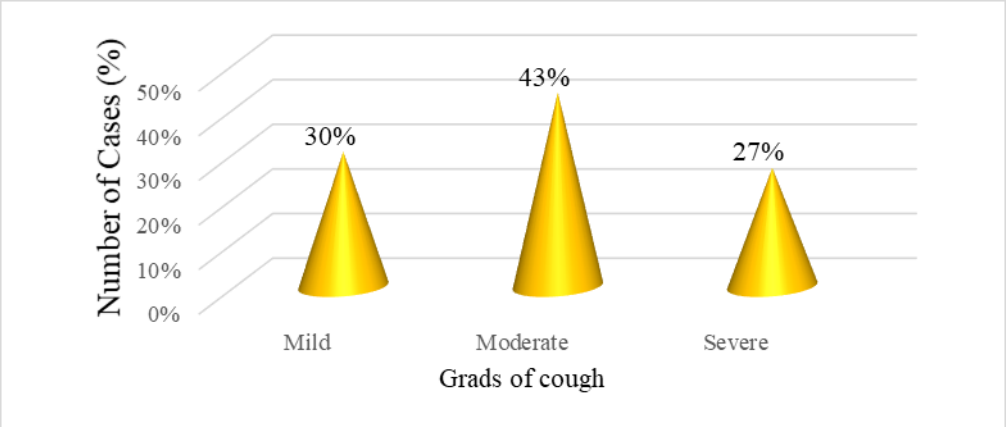
In the present study, there are 1 (1%) subjects < 90 cm height, 37 (45%) subjects have 91 – 100 cm height, 35 (42%) subjects have 101 – 110 cm height and 10 (12%) subjects have 111 – 120 cm

height. The height among the participants varied from 90 to 120 cm. (table 6.4). The height was negatively correlated with R at 5Hz and its correlation coefficient was -0.4156 (table 6.15). It indicates that as the height increases the airway resistance decreases. Asumpcao et al[85] have found similar correlation between height and R^2 for all impulse oscillometric parameters (46.51 %.). As suggested by ATS/ERS statement for pulmonary function testing in preschool children, it indicates that most of the children were in 91-100 and 101 to 110 cm height[6]. Hence the results are applicable to children with these height groups.

6.6 Frequency distribution of cough

Table 6.5: Frequency distribution of cough. (n = 83)

Cough	Frequency	%
Mild	25	30%
Moderate	36	43%
Severe	22	27%



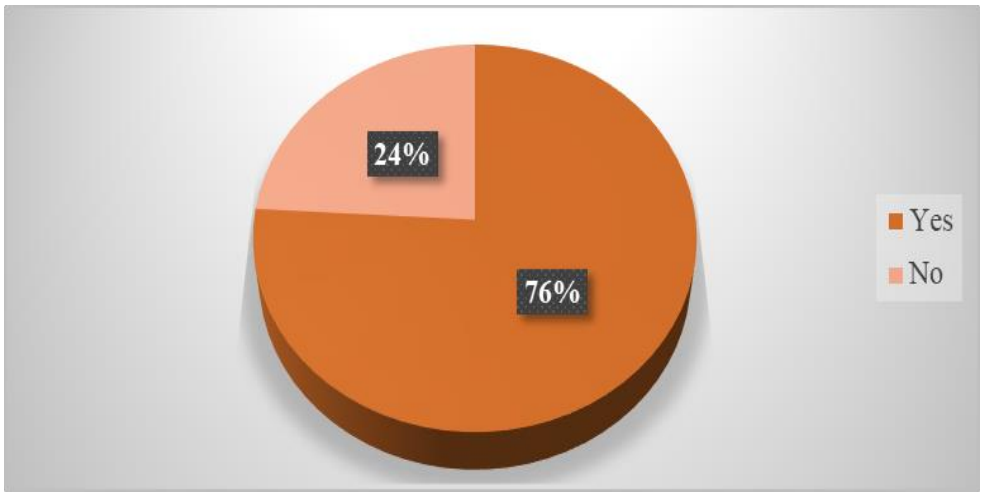
Graph 6.5: Frequency distribution of cough.

From Table 6.5, it is concluded that, 25 (30%) patients have mild cough, 36 (43%) patients have moderate cough and 22 (27%) patients have severe cough. Cough was predominant symptom in all the patients. Moderate cough as per the parental rating was very common (Table 6.5). In 1981 and 1982 Cloutier[98] and Hannaway et al[99] described children who presented with cough and they thought the patient is suffering from asthma. These children responded well to bronchodilators. They did not present with wheeze. Fever and cough are clinical symptoms which may be present in pneumonia. Pneumonia may not present with cough if disease is confined to alveoli as alveoli do not have many cough receptors. In a study by Murphy et al[100] 5.3% children had pneumonia with history of fever and cough without having breathlessness or respiratory distress. Thus cough may be a symptom of either pneumonia or wheezing episode.

6.7 Frequency distribution of cold

Table 6.6:Frequency distribution of cold. (n = 83)

Cold	Frequency	%
Yes	63	76%
No	20	24%



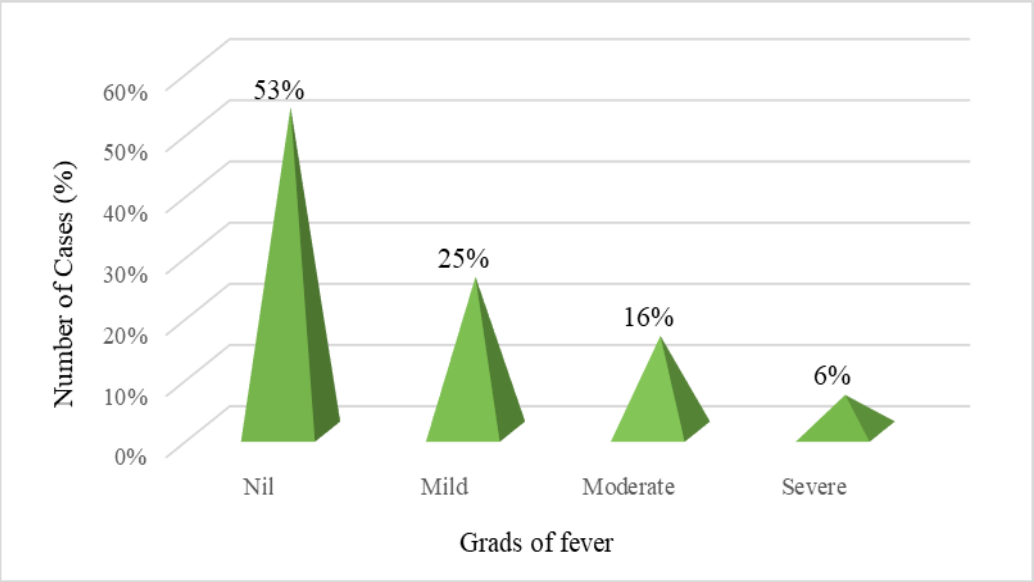
Pie chart 6.6: Frequency distribution of cold.

In the present study, there are 76% subjects having cold remaining do not have cold (Table 6.6). Respiratory viral infections have been shown to giving rise to airway hyper reactivity. This is well documented by the article by Stark et al[101] in respiratory viral infections and airway hyper reactivity in children. It has been shown that after viral infection the hyper reactive airway may develop after 48-72 hours in this children.[102]

6.8 Frequency distribution of fever

Table 6.7: Frequency distribution of fever. (n = 83)

Fever	Frequency	%
Nil	44	53%
Mild	21	25%
Moderate	13	16%
Severe	5	6%



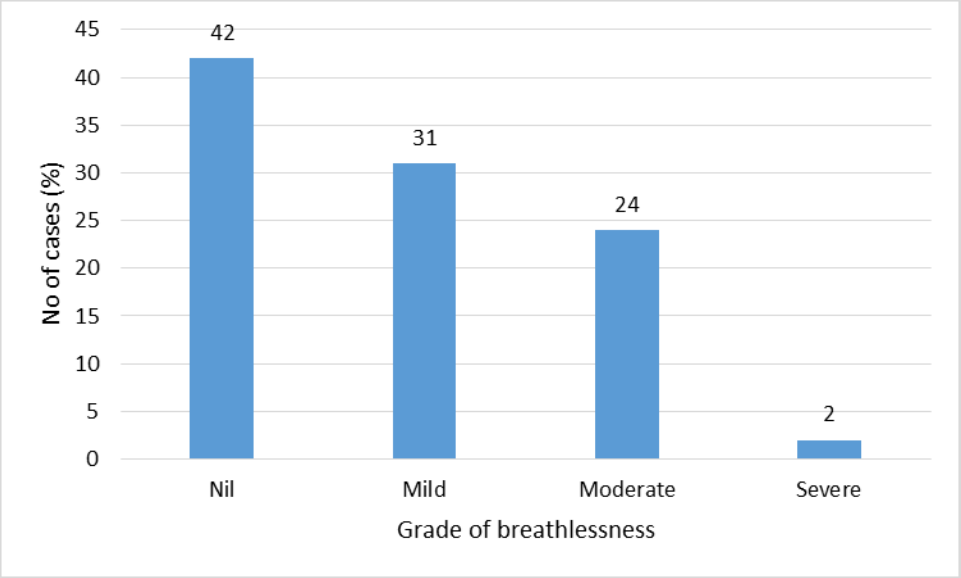
Graph 6.7: Frequency distribution of fever.

In the present study, 21 (25%) subjects had mild fever, 13 (16%) subjects had moderate fever and 5 (6%) had severe fever. Mild to moderate fever was common in these patients with no severe respiratory diseases (Table 6.7). High grade fever is associated with pneumonia but may be present in viral infections. Thus fever may not be a differentiating feature in various respiratory diseases. In children under 5 years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is clinically suspected by fast breathing or indrawing of chest wall. During inhalation movement of chest is inside rather than outside which is called as indrawing.[7] WHO criteria also does not include fever in the diagnostic criteria of pneumonia.

6.9 Frequency distribution of breathlessness

Table 6.8: Frequency distribution of breathlessness. (n = 83)

Breathlessness	Frequency	%
Nil	35	42%
Mild	26	31%
Moderate	20	24%
Severe	2	2%



Graph 6.8: Frequency distribution of breathlessness.

In the present study, there are 26 (31%) subjects have history of mild breathlessness, 20 (24%) subjects have moderate breathlessness and 2 (2%) have severe breathlessness. Mild to moderate breathlessness was present in most of the patients (Table 6.8). Respiratory distress is the result of inadequate supply of oxygen due to failure of oxygenation and/or ventilation. In children,

respiratory distress presents as signs of increased work of breathing. It is manifested by tachypnea, nasal flaring, and use of accessory muscles, and/or chest retractions as per the PALS manual. Breathlessness or tachypnea has been linked to pneumonia by WHO.[24.] Wheezing episodes are also associated with increased respiratory rate and are classified as pneumonia as per WHO criteria. Hence WHO has advised to give inhaled bronchodilator and then reclassify the disease. But further evaluation is not done in WHO guidelines. Thus presence of breathlessness is usually associated with respiratory diseases in children but etiological diagnosis cannot be made on its basis. This is because of lack of objective evidence to differentiate between pneumonia (alveolar disease) and wheezing episode (disease of airways). As the etiology is viral, lot of children are unnecessary given antibiotics. These children also require further follow up about recurrent wheezing episode where they will require inhaled corticosteroids or allergen avoidance. This service is not provided due to lack of objective evidence to diagnose wheezing episode.[8]

6.10 Respiratory rate and heart rate

Table 6.9 Heart rate and respiratory rate mean and SD

Variable	Mean	SD
HR	112.17	16.87
RR	35.36	7.26
SPO2	0.97	0.016

In the present study respiratory rate was increased in most of the patients and heart rate was also increased. (Table 6.9)

6.11 Rhonchi and crepts and final diagnosis

Table 6.10: Distribution of rhonchi and crepts with final diagnosis.

Rhonchi and crepts	Wheezing Episode	Pneumonia
Rhonchi	26	7
Crepts	1	24

In the present study out of 36 children with wheezing episode 26 patients had rhonchi on auscultation. This indicates moderate correlation with final diagnosis. (Table 6.10) 24 cases out of 39 cases of pneumonia had crepitations. The auscultation forms the easy and safe method for diagnosis of pneumonia.[103] In acute pneumonia crackles are mid inspiratory and coarse.[104] They are more end inspiratory during resolution of pneumonia. The lung parenchyma gradually becomes drier and stiffer due to reduction in edema and healing process during resolution of pneumonia. More pressure is required to open airways. Due to this crackles are heard towards end inspiratory phase and are fine in nature.[103]

In a study by Saeed et al[105] in emergency department in adults, they found that auscultation is not a reliable way of diagnosing pneumonia in emergency department. The inter observer variability is very high.

In a study by Florin et al[106] it was observed that the inter rater reliability of examination findings in patients with suspected community acquired pneumonia was not good for any signs or symptoms. The inter rater reliability for wheezing, retractions was between 0.6-0.8. Respiratory rate and crackles had inter rater reliability between 0.4 to 0.6.

Scrafford et al[107] have tried to use digital stethoscope to improve the diagnostic accuracy of diagnosis of pneumonia and compared the findings with chest radiographs. The sensitivity of digital auscultation was 56% and specificity was 73%. They concluded that digital auscultation may be helpful in improving the specificity of pneumonia diagnosis.

6.12 X-ray diagnosis and final diagnosis

Table 6.11: X-Ray diagnosis and final diagnosis.

X-Ray	Wheezing Episode	Pneumonia
Pneumonia	13	16
Wheezing episode	0	1

X-ray chest in the present study could diagnose 16 out of 39 pneumonias. But x-ray chest did not show significant changes in wheezing episodes. Chest radiograph is not routinely advised in non severe pneumonia. In a study by Swingler et al[108] 522 children in age group of 2months to 59 months diagnosed by WHO criteria for pneumonia were randomly allocated to have chest x-ray or not. They

concluded that the use of chest radiographs did not have impact on time to recovery or subsequent visit to health facility. The clinician's experience could not modify this absence of effect of x-ray chest. Thus the conclusion was that chest radiographs should not be done routinely. (Table 6.11).

World health organization has developed chest x-ray guidelines for the diagnosis of pneumonia. It indicates different entities such as consolidation. The end point consolidation: a dense opacity that may be consolidation. Non end point shadows such as lacy infiltrate with peribronchial thickening and areas of atlectasis. This protocol had concordance of 0.87 between pediatrician and radiologists.[109] In the present study the x-rays were read by radiologists.

Grady et al[10l] in their paper concluded that the x-ray chest is widely used tool for diagnosis of pneumonia but it is imperfect. Its utility depends on the setting, the clinical presentation, experience of the clinician and radiographer and the epidemiology of the source population.

6.13 Demographic and symptom analysis and final diagnosis

Table 6.12: Demographic and symptom analysis according to final diagnosis.

Variable		Wheezing Episode N=36		Pneumonia N=39		Others N= 8		P-value
		n	%	n	%	n	%	
Sex	Female	18	50%	14	36%	4	50%	0.433
	Male	18	50%	25	64%	4	50%	
Cough	Mild	9	25%	10	26%	6	75%	0.2942
	Moderate	17	47%	17	44%	2	25%	
	Severe	10	28%	12	31%	0	0%	
Cold	Yes	30	83%	26	67%	7	88%	0.1743
	No	6	17%	13	33%	1	13%	
Fever	Nil	20	56%	18	46%	6	75%	0.4856
	Mild	10	28%	9	23%	2	25%	
	Moderate	5	14%	8	21%	0	0%	
	Severe	1	3%	4	10%	0	0%	
Breathlessness	Nil	14	38%	20	51%	1	12%	0.2942
	Mild	8	22%	13	33%	5	62%	
	Moderate	12	33%	6	15%	2	25%	
	Severe	2	6%	0	0%	0	0%	

The correlation of symptoms was not found with the final diagnosis. Symptoms stated by the parents do not always correlate with the final diagnosis. (Table 6.12)

6.14 Analysis of Impulse oscillometry parameters

Table 6.13: Analysis of impulse oscillometry parameters by Paired-T Test and Wilcoxon-Sign-Rank Test.

Variable	Mean ± SD		P-value
	Pre-Nebulization	Post-Nebulization	
VT	0.26 ± 0.09	0.34 ± 0.64	0.00035
AX	4.98 ± 5.43	3.91 ± 4.35	1.12E-05
Z.AT.5 Hz.	1.20 ± 0.73	1.09 ± 0.62	6.87E-05
R.AT.5 Hz.	1.08 ± 0.43	0.99 ± 0.34	0.0002
R.AT.10 Hz.	0.77 ± 0.22	0.71 ± 0.21	0.00037
R.AT.20 Hz.	0.56 ± 0.19	0.54 ± 0.17	0.0417
X.AT.5 Hz.	-0.41 ± 0.69	-0.36 ± 0.58	0.0132
X.AT.10 Hz.	-0.35 ± 0.36	-0.29 ± 0.31	7.54E-05
X.AT.20 Hz.	-0.13 ± 0.14	-0.08 ± 0.12	6.72E-08
RES.FREQ.	24.69 ± 5.07	23.53 ± 5.42	0.0005

From table 6.13, conclude that, at 5 % level of significance,

- Mean difference in pre- nebulization and post- nebulization of area under Curve ($p < 0.05$).is significant.
- Mean difference in pre- nebulization and post- nebulization of resistance at 5Hz ($p < 0.05$) is significant.

- Mean difference in pre- nebulization and post- nebulization of reactance at 5Hz ($p < 0.05$) is significant.
- Mean difference in pre- nebulization and post- nebulization of reactance at 20Hz ($p < 0.05$) is significant.

  Significant mean difference in pre- nebulization and post- nebulization of resonant frequency ($p < 0.05$).

Impulse oscillometry has been correlated with spirometry and other lung function tests in various studies[78, 92]. There are studies which were carried out to find the impulse oscillometry parameters in pre and post bronchodilatation in healthy children.

In the study by Laura Gochioka Rangel[86] the age group was 4-15 years of age in healthy Mexican children. There mean value of R at 5 Hz was 0.67 kPa /lit/s. This indicates that the values in older and healthier children are less than the younger children as well as in children with wheezing episode. In their study there was no difference between male and females were observed. Mean R at 5Hz was 0.66 kPa/lit/s in males and 0.67 kPa /lit/sec in females.[86, 87]

Very few studies are there in children with respiratory symptoms to evaluate actual use of impulse oscillometry in office practice**.**

In present study the parameters of impulse oscillometry were as follows. R at 5 Hz pre and post nebulization there was a significant change (p value was <0.0002) (Table 6.13). Pre nebulization mean value was 1.08 kPa /lit/sec and post nebulization mean value was 0.99 kPa /lit/sec. This is slightly higher than the levels observed by Konstantinou and Papadopoulus[94]. This is because of the age group 4-6 years in their study group. Our study

group comprised of 3 to 6 years of age. The values are usually higher in lower age group. Konstantinou[94] has also calculated in children with wheezing episodes, in the present study all the children were not suffering from wheezing episode**.**

Table 6.14: Studies showing values of R at 5 Hz before and after bronchodilation.

Studies	**Baseline Pre-bronchodilatation**	**Post-bronchodilatation**
	R at 5 Hz	R at 5 Hz
Konstantinou[94]	0.943 ± 0.269	0.817 ± 0.227
Present study	1.08 ± 0.43	0.99 ± 0.34(table 13)
Nielsen et al[111]	1.24 ± 0.29	1.01 ± 0.25
Klug[92]	1.48 ± 0.25	1.25 ± 0.22

Above values are in KPa/L/s units.

Klug et al[92] carried out the impulse oscillometry, interruptor technique and body plethysmography in 2-5 year old stable asthmatic children. The value of R at 5 Hz was higher than the present study and difference after bronchodilator use was also more. This is likely because of the lower age group and all the children were stable asthmatic children.

Batmaz et al[89] conducted comparative study of children in the age group of 6 yrs of age to 17 yrs of age by impulse oscillometry and spirometry in acute asthmatics, stable asthmatics and healthy children. The values they found were R at 5 Hz 0.86 ±

0.24 in acute asthmatics, 0.74 ± 0.22 in stable asthmatics and in healthy subjects 0.67 ± 0.19 kPa/lit/s. These values were lower than the values in present study as the age group was higher (6 years to 17 years). The above study concluded that the impulse oscillometry values correlated with spirometry and can be used for similar purpose.

Knitillha et al[91] in a retrospective study measured R at 5 Hz at the age of 2-7 years and followed the patients and measured lung function by spirometry. They found that there was a correlation between R at 5 Hz values and spirometric parameters.

Thus from all above studies, it is clear that childhood impulse oscillometry value of R at 5Hz is correlated with spirometry at the later age group. Also the values change according to age and are different in normal healthy children and during wheezing episode or asthma attack.

In present study X at 5 Hz mean value was found to be -0.41± 0.69 which changed to -0.36 ± 0.58. (P value <0.05)

Table 6.15: Values of X at 5 Hz before and after bronchodilation.

Studies	Pre – bronchodilaton	Post-bronchodilation
	X at 5 Hz	X at 5 Hz
Present study	-0.41 ± 0.69	-0.36 ± 0.58 (table 6.13)
Klug[92]	-0.59 ± 0.22	-0.43 ± 0.14
Nielsen[112]	-0.44 ± 0.16	-0.31 ± 0.09

Above values are in kPa/L/s units. X at 5Hz = Respiratory Reactance at 5Hz.

X at 5 Hz has been studied by Klug et al[92] and found to be slightly higher than present study. As in case of R at 5 Hz the age group of the study was lower than present age group. The children were all with history of recurrent wheeze. Due to this also the X at 5Hz is higher in this study. But the change after bronchodilatation is significant. Thus the compliance of the lung also changes after the bronchodilatation. The negative portion of reactance (X at 5 Hz) becomes more negative if the compliance increases, the inertive portion is positive, thus, it is clear that bronchodilators increase compliance.

Thus impulse oscillometry not only demonstrates resistance of airways but also compliance, a lung parameter not easily available with other investigations.

The resonant frequency measured in this study was:

Table 6.16: Resonant frequency before and after bronchodilation.

Mean Resonant frequency ± SD		P-value
Pre-Nebulization	Post-Nebulization	
24.69 ± 5.07	23.53 ± 5.42	0.0005

This is also statistically significant as p value is <0.0005. It indicates that the resonant frequency improves significantly after bronchodilatation. Similar changes have been observed by Marotta et al[3] in asthma. But it was found to be insignificant.

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6.15 Impulse oscillometry parameters and final diagnosis

Table 6.17: IOS Parameters in wheezing episode and pneumonia

IOS Parameters	Wheezing episode N=36	Pneumonia N=39	P-value
	Mean (95% CI)	**Mean (95% CI)**	
Before Nebulization R at 5 Hz	1.23 (1.20, 1.26)	1.04 (1.02, 1.05)	0.07256
After Nebulization R at 5 Hz	1.04 (1.01, 1.06)	1.02 (1.00, 1.03)	0.9029
ΔR5 Hz (%)	0.36 (0.33, 0.37)	0.12 (0.11, 0.13)	< 0.0001
Before Nebulization R at 20 Hz	0.63 (0.62, 0.65)	0.54 (0.52, 0.55)	0.0677
After Nebulization R at 20 Hz	0.57 (0.55, 0.58)	0.55 (0.54, 0.56)	0.9076
ΔR20 Hz (%)	0.18 (0.16, 0.19)	0.12 (0.11, 0.13)	0.3785
Before Nebulization X at 5 Hz	-0.51 (-0.49, -0.55)	-0.37 (-0.35, -0.38)	0.2963
After Nebulization X at 5 Hz	-0.45 (-0.43, -0.47)	-0.33 (-0.32, -0.36)	0.7279
ΔX5 Hz (%)	2.84 (2.12, 3.56)	2.44 (1.74, 3.14)	0.007548

Before Nebulization X at 20 Hz	-0.18 (-0.17, -0.19)	-0.086 (-0.074, -0.098)	0.008413
After Nebulization X at 20 Hz	-0.10 (-0.09, -0.11)	-0.074 (-0.072, -0.077)	0.8684
ΔX20 Hz (%)	-273.10 (-271.8, -275.12)	-244.23 (-242.2, -246.80)	0.9511
Before Nebulization Ax value	6.68 (6.21, 7.15)	4.23 (4.13, 4.33)	0.09549
After Nebulization Ax value	4.61 (4.22, 5.00)	3.76 (3.67, 3.87)	0.8377
ΔAX	2.84 (2.62, 3.05)	0.96 (0.91, 0.99)	<0.0001
Before Nebulization Resonant Frequency	26.31(25.96, 26.66)	23.29(23.15, 23.44)	0.0172
After Nebulization Resonant Frequency	24.49(24.08, 24.90)	22.94(22.79, 23.08)	0.4734
Δ Resonant Frequency	3.26 (3.10, 3.41)	1.68 (1.61, 1.74)	0.02437

If R at 5 Hz is considered in wheezing episode and pneumonia the mean value for R at 5 Hz is 1.23 (CI 1.20, 1.26) and mean value of R at 5 Hz for pneumonia 1.04 (CI 1.02, 1.05), it is significant and the change in R at 5 Hz is significant (p value is <0.0001). It indicates that there is difference in baseline values of R at 5 Hz in wheezing episode and R at 5 Hz in pneumonia. The change in R at 5 Hz in wheezing episode is significant and it is not significant in pneumonia cases (Table 6.17).

In the similar way, change in X at 5 Hz is significant in wheezing episode but not in pneumonia. The change in parameter AX is also similarly significant between wheezing episode and pneumonia. The change in resonant frequency is also significant in wheezing episode but not in pneumonia (Table 6.17).

These differences in R at 5 Hz, X at 5 Hz, Ax and resonant frequency in wheezing episode and pneumonia indicate that these parameters of impulse oscillometry can differentiate between wheezing episode and pneumonia (Table 6.17).

The final diagnosis in this study by using clinical examination and impulse oscillometry system and follow up of patient was 36 patients with wheezing episode and 39 patients with pneumonia and other diagnosis were present in rest of the cases.

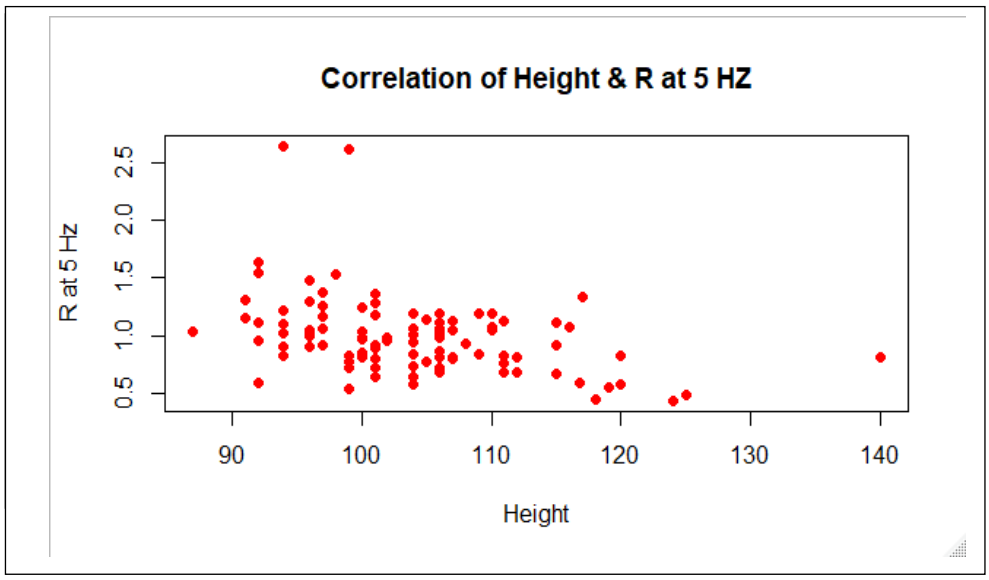
6.16 Correlation of height and weight with R at 5 Hz

Table 6.18: Correlation of height and weight with Post R at 5 Hz.

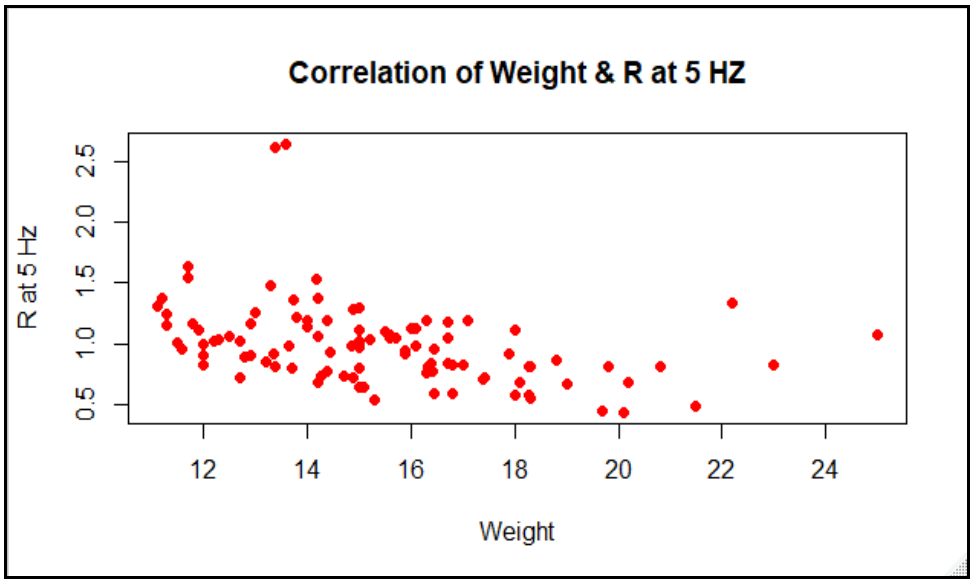
Variable	Correlation	P-value
Height	-0.4156	**1.55e-05**
Weight	-0.4738	**5.61e-07**

In the present study, the variable height is negatively correlate with R at 5 Hz, with its correlation coefficient value is -0.4156.

Also, the variable weight is negatively correlate with R at 5 Hz, with its correlation coefficient value is -0.4738.



Graph 6.9: Correlation plot between height and R at 5 HZ



Graph.6.10: Correlation Plot between weight and R at 5 HZ

6.17 Logistic regression analysis for prediction of diagnosis

Logistic regression analysis for prediction of diagnosis:

In the study "Clinical Presentation and Impulse Oscillometry to Differentiate between Wheezing Episode and Pneumonia in children"**,** there are two types of diagnosis wheezing episode and pneumonia, and for predicting the diagnosis based on different variables (factors) the logistic regression classifier technique is used.

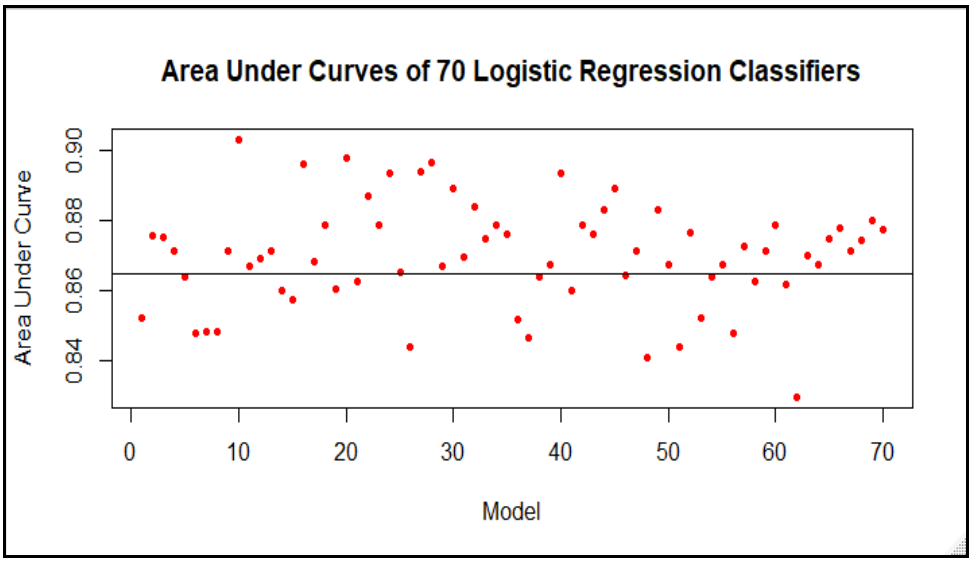
Before performing the logistic regression for prediction of diagnosis the given data is unbalanced. To balance the data ***'Synthetic Oversampling Technique'*** (https:// arxiv. org/pdf/ 1106. 1813. pdf) was used and the data was balanced. Now, the balanced data was simulated 70 times, and the logistic regression classifier for prediction of diagnosis is built on each simulated data. After modelling one must check the performance of classifiers. The performance (good / bad) of classifier is based on scatter plot of area under curve of each logistic regression model.

Table 6.19: Univariate logistic regression model for prediction of diagnosis.

Variable		Estimate	z value	P-value
Intercept		14.80121	0.825	0.409384
Sex	Female	Reference		
	Male	0.67771	1.553	0.120306
Cough	Level-1	Reference		
	Level-2	0.38635	0.727	0.467489
	Level-3	-0.88617	-1.411	0.158385

Cold	Level-1	Reference		
	Level-2	-1.73283	-3.11	0.001869
	Level-3	-0.51332	-0.375	0.707605
Fever	Level-1	Reference		
	Level-2	-2.47764	-4.184	**2.86E-05**
	Level-3	-4.25546	-4.234	**2.30E-05**
	Level-4	-20.20036	-0.014	0.989044
Breathlessness	Level-1	Reference		
	Level-2	-0.05368	-0.113	0.910294
	Level-3	0.18241	0.271	0.786685
	Level-4	40.51804	0.015	0.987841
HR		0.03708	2.465	**0.013695**
RR		0.08319	2.226	**0.025991**
SPO2		-5.22263	-0.291	0.771035
VT		4.72527	1.31	0.190185
AX		3.17399	3.927	**8.60E-05**
Z AT 5 HZ		-1.69642	-0.315	0.753024
R AT 5 HZ		-14.40928	-2.542	**0.011034**
R AT 10 HZ		1.1578	0.189	0.850063
R AT 20 HZ		15.10214	2.609	**0.009074**
X AT 5 HZ		12.93902	3.71	**0.000207**
X AT 10 HZ		10.70827	2.082	**0.037319**
X AT 20 HZ		-27.5895	-2.955	**0.003123**
RES.FREQ		-0.75918	-4.021	**5.79E-05**

The highlighted p-value shows significant.



Graph 6.11: Performance of logistic regression classifier

By observing the above scatter plot, we can see that most of the area under curve values are between 0.84 to 0.90. Therefore, logistic regression classifiers are good for prediction of diagnosis.

The ***Accuracy*** of above model is ***0.8676.***

The ***Sensitivity*** of the above model is ***0.8611.***

The ***Specificity*** of the above model is ***0.8750.***

The ***Area Under Curve*** of the above model is ***0.8715.***

Note: Data was simulated for 70 times and this logistic regression model is randomly selected from those 70 simulations.

Regression Model is Given Below,

*Y (Wheezing Episode) = 14.80121 + 0.67771 * (Male) + 0.38365 * Cough (Level-2) – 0.88617 * Cough (Level-3) – 1.73283 * Cold (Level-2) – 0.51332 * Cold (Level-3) – 2.47764 * Fever (Level-2) – 4.25546 * Fever (Level-3) – 2.20036 * Fever (Level-4) – 0.05368 * Breathlessness (Level-2) + 0.18242 * Breathlessness (Level-3) +*

*4.51804 * Breathlessness (Level-4) + 0.03708 * HR + 0.08319 * RR – 5.22263 * SPO2 + 4.72527 * VT + 3.17399 * AX – 1.69642 * Z.At.5.Hz. – 14.40928 * R.At.5.Hz. + 1.1578 * R.At.10.Hz. + 15.10214 * R.At.20.Hz. + 12.93902 * X.At.5.Hz. + 10.70827 * X.At.10.Hz. – 27.5895 + X.At.20.Hz. – 0.75918 * RES.FREQ.*

6.18 percentage change in R at 5 Hz and final diagnosis

Table 6.20 A: Contingency table between percentage changes in R at 5 Hz and final diagnosis.

Percentage change in R5	**Clinical diagnosis wheezing episode positive**	**Clinical diagnosis wheezing episode negative**
Change in R at 5 Hz >25%	24	8
Change in R at 5 Hz <25 %	12	39

Table 6.20 B:

Statistics	**Percentage Change in R5**
Sensitivity	66.67
Specificity	82.98
PPV	75.00
NPV	76.47
Accuracy	75.90

The cut off suggested by change in R at 5 Hz by Hellinckx was 40%, as they found change in R at 5 Hz even in non wheezing children.[77] But if we take history and impulse oscillometry together the diagnostic accuracy can be increased. Marotta et al[3] noted a cutoff point in the range of 20% to 24% which could distinguish most of the asthmatic group in four year old children.

6.19 Development of scoring system

Regression model used to develop scoring system

*Y (Wheezing Episode) = 0.84 + 0.52 * Age (> 3.5) + 0.45 * Cough (Moderate) + 0.52 * Cough (Severe) – 0.03 * Cold (Moderate) + 0.95 * Cold (Severe) + 0.28 * Fever (Mild) – 0.07 *Fever (Moderate) + 0.63 * Fever (Severe) + 0.78 * Breathlessness (Mild) + 0.92 * Breathlessness (Moderate) + 0.82 * Breathlessness (Severe) + 4.84 * % Change in R5 (> 25) + 3.46 * % Change in R20 (> 20) + 3.59 * % Change in X5 (> 15) + 1.88 * Delta AX (> 70) + 0.75 * Delta Res. Freq (> 15)*

A logistic regression analysis was performed, the area under curve was found to be between 0.8715. Thus it is a good model to diagnose wheezing episode.

The accuracy of above model is 0.8676**.** The sensitivity of the above model is 0.8611. The specificity of the above model is 0.8750. The area under curve of the above model is 0.8715.

Thus, the specificity and sensitivity are above 80% suggest a good regression equation.

Scoring system is helpful in clinical medicine to differentiate between the various differential diagnoses. Regression analysis for scoring system was based on clinical presentation and change in parameters after bronchodilation. The scoring system was developed by considering the numeric and categorical variables. Numeric variables were converted to factor variables according to cutoff points. The regression coefficients that are estimated by multiple regressions are used to assign scores when outcome is quantitative. For qualitative outcomes logistic regression coefficients are used. On the degree of increasing magnitude arbitrary scores are assigned. Finally total score is calculated or each subject to represent prediction of outcome probability.

Table: 6.21 Scoring System is for predicting wheezing episode:

Risk Factors	Score
Age (> 3.5)	1
Cough (Moderate)	0
Cough (Severe)	1
Cold (Moderate)	0
Cold (Severe)	1
Fever (Mild)	0
Fever (Moderate)	0
Fever (Severe)	1
Breathlessness (Mild)	1
Breathlessness (Moderate)	1

Breathlessness (Severe)	1
% Change in R5 (> 25)	5
% Change in R20 (> 20)	3
% Change in X5 (> 15)	4
Change in AX (> 70 %)	2
Change in Res. Freq (> 15 %)	1

From the above, scoring system is divided into 3 categories.

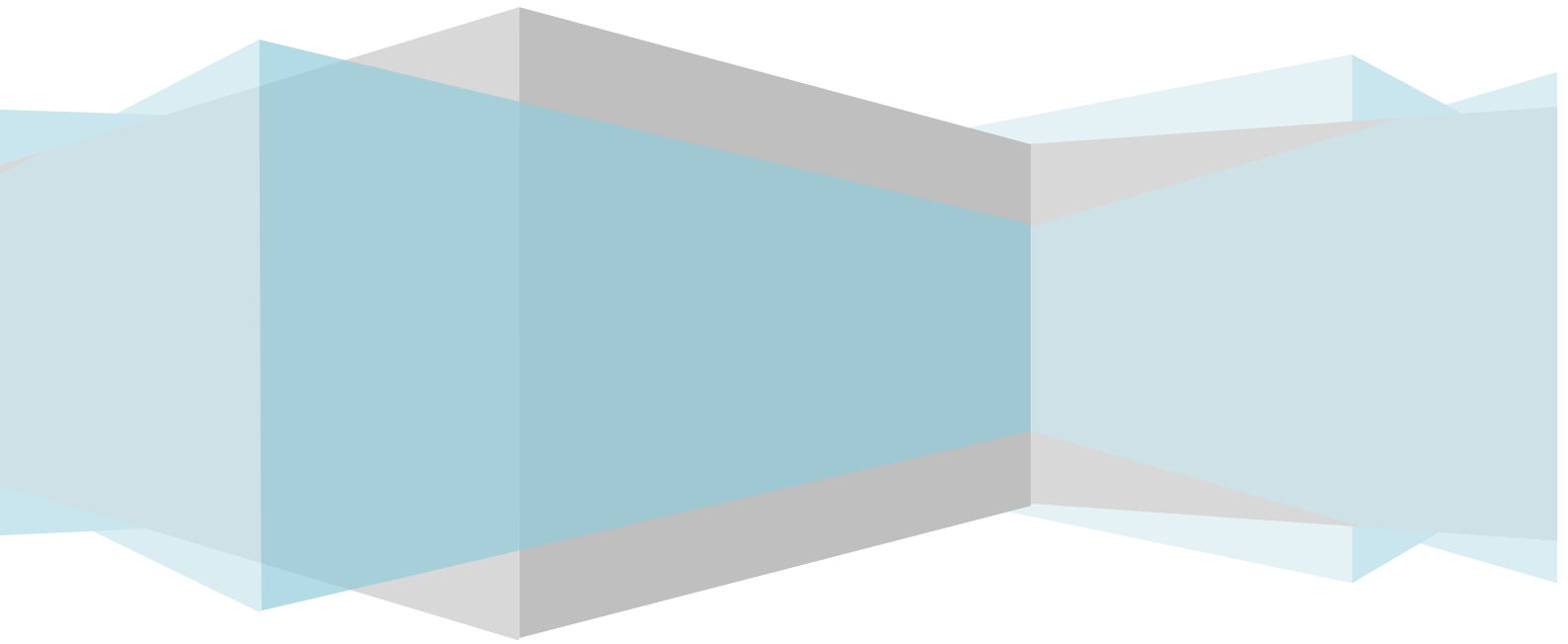
Table 6.22: Categories of wheezing episode.

Wheezing Episode	Score
Mild	>7
Moderate	8-11
Severe	11-22

The following are the values used when the above scoring system is used to predict wheezing episode from the available data.

Also, from the above scoring system, it is clearly depicted that, *Breathlessness, % Change in R5 (> 25), % Change in R20 (> 20), % Change in X5 (> 15)* are closely related for getting the wheezing episode. The limitation of the scoring system in this study is, it is not validated, which will be done subsequently.

CHAPTER-VII
SUMMARY AND CONCLUSIONS



SUMMARY AND CONCLUSIONS

Chapter 1: Respiratory problems are the commonest cause of morbidity and mortality in children. As the infective causes due to bacterial infections are decreasing, the respiratory problems due to viral infections and allergies are increasing relatively. The diagnosis of these conditions objectively is difficult due to non availability of a test which can be performed. Measurement of lung function is essential part of evaluation in older children and adult by spirometry. Due to lack of such test children below six years are treated empirically depending on history and clinical examination. Previously cases of pneumonia were more hence use of antibiotics was advised in every child with lower respiratory problem. Presently respiratory tract problems with infections are decreasing. Hence there is need to assess lung function even in small children so as to make a proper diagnosis and proper treatment. Impulse oscillometry system is a machine which can be used to assess lung function in children with minimum co-operation. The main advantage is it does not require forceful mannouvres. A scoring system to differentiate between pneumonia and wheezing episode may be useful for further evaluation and treatment of children with respiratory diseases.

Chapter 2: The aim and objectives of this research are given in this chapter. The aim is to differentiate between wheezing episodes and pneumonia in 3-6 years old children with clinical presentation and pulmonary function testing with impulse oscillometry. The objective of developing scoring system was kept to find out whether clinical presentation along with impulse oscillometry parameters can help in the diagnosis.

Chapter 3.1: In this chapter information regarding current status of pneumonia epidemiology and mortality is given. Even today pneumonia is a major killer in children less than five years. This mortality is more in developing countries. The fact that child mortality due to other causes has decreased but not due to pneumonia indicates that further research in the investigations, diagnosis and treatment of pneumonia is needed. First and foremost is not to consider every respiratory problem as pneumonia. There is vast difference in hospital based case fatality and community based case fatality in pneumonia. Therefore there is need to treat pneumonia with oxygen and implement new strategies for diagnosis and treatment of pneumonia. Unfortunately pneumonia in children is on low priority in many countries as compared to HIV and malaria. The clinical presentation of pneumonia varies according to pathogen, host and severity. No symptom or sign is sufficient to make a diagnosis of pneumonia in children. In infants and children symptoms and signs of pneumonia are not easily obvious. Presence of fever and cough is considered as pneumonia. But cough may appear later and fever may not be present in certain types of pneumonia and in malnourished cases. In infants pneumonia may manifest as feeding difficulty or restlessness.

In a review it was seen that fever, increase respiratory rate and auscultatory findings did not correlate with pneumonia. Severe pneumonia are diagnosed by these signs and symptoms but non severe pneumonia may not correlate with criteria of increased respiratory rate or indrawing. Clinical examination showing bronchial breathing and presence of crepitations is useful in

diagnosis of pneumonia but it may not be present in all children with pneumonia. Radiological examination was supposed to be gold standard for diagnosis of pneumonia but they may not be seen in initial days. Atypical pneumonia may have different clinical presentation.

Chapter 3.2: Various phenotypes described in wheezing children are discussed in this chapter. The Tucson study described three phenotypes early wheezers, persistent wheezers and late onset wheezers. Early wheezers tend to improve with advancing age. It was observed that lung function in persistent and late onset wheezers decreased by the six years of age. Hence it was thought that can we decrease deterioration of lung function in these children by identifying them early.

The European society's task force made a different classification of episodic wheeze and multi-trigger wheeze. Episodic wheeze was thought of due to virus induced and multi-trigger wheeze due to atopy and other irritants such as tobacco smoke. As per GINA guidelines wheeze may be interpreted differently by parents and caregivers. There is no standardized test in children which can diagnose bronchospasm objectively. The tests which are used are therapeutic trial, tests of atopy, chest x-ray, lung function tests, ex-haled nitric oxide and risk profiles. GINA - guidelines 2018 has advised about prevention of wheezing episode. It is thought that 'a window of opportunity 'exists to prevent wheezing in children. Ingestion of certain foods causing allergy by mother may help in decreasing wheezing episodes in children but no standard advice is yet finalized. Breast feeding, vitamin D supplementation and

delayed introduction of solid food have been implicated in protection from wheezing episodes. Exposure to allergens, maternal smoking is likely to give rise to wheezing in children. Vaginal delivery may be beneficial. Antibiotic use during pregnancy and after delivery is associated with increased wheezing. Recently respiratory pathogens Respiratory Syncytial virus and Rhino viruses have been implicated in development of wheezing episode and asthma and various mechanisms have been described. The need for objectively diagnosing wheezing episode has been explained.

Chapter 3.3: There is a change in the epidemiology of respiratory problems. Several studies have brought into notice that the guidelines recommended by IMCI if used in practice can lead to more patients treated with antibiotics as it lead to increased diagnosis of pneumonia. The symptoms and signs of asthma in young children are similar to recurrent lower respiratory tract infections, such as bronchitis, bronchiolitis, and pneumonia. Bronchodilators are not useful in bronchiolitis. A separate treatment algorithm should be developed for children suffering from wheeze. The majority of later diagnosed cases of asthma begin before 3 years of age and up to 80% before the age of six years. Currently there is no objective measure of measuring severity of the wheezing episode. Hence there is need to develop objective method of measuring the severity of bronchial hyper responsiveness and as well as frequency of number of episode. The quality of life of children with wheezing and asthma is affected very much. The quality of life of their families is also affected. Hence there is need to diagnose wheezing episodes objectively.

Chapter 3.4: There are various causes of wheezing in children. In preschool children bronchial asthma, bronchiolitis and pneumonia can give rise to wheezing. The rare causes are inhaled foreign bodies and compression of airways from outside by lymph nodes or tumour. Wheezing is very common symptom in children below five years. Children with wheeze may have fast breathing and/or chest indrawing. Therefore, they may be categorized as pneumonia or severe pneumonia. Thus using WHO/IMCI algorithm leads to over diagnosis of pneumonia. In various studies performed in India and outside it was seen that asthma was diagnosis in fifty percent of the cases and pneumonia in one third cases. The incidence of wheezing was found to be 22% to 75%. The incidence of wheezing was higher in children presenting with indrawing. Thus it is clear that wheezing may be present in many children with fast breathing and chest in drawing. The diagnosis of wheeze is made only when audible wheeze is present. It has been found that audible wheeze is found in only 29.3% of children when compared to auscultable wheeze. The present method of treating the patients on audible wheeze leads to underutilization of bronchodilators and increased treatment with antibiotics. Therefore there is need to diagnose wheeze by skilled personnel.

Chapter 3.5 Literature review regarding impulse oscillatory system is described in this chapter. Impulse oscillometry system can be used to diagnose wheezing objectively in three to six years old children. The changes in lung function are assessed by putting a sound wave in the airway hence the stimulus can be modified from outside without asking the patient to do any particular manouvre. In impulse

oscillometry the resistance is measured by sending a pressure wave applied externally and measuring the respiratory airflow. External pressure wave generator produces artificial impulse-shaped test signals of multifrequency. The pneumotachograph and transducer measure airway opening pressure and airflow to calculate respiratory impedence (Zrs). Low frequency pressure waves are transmitted to the periphery and high frequency waves can travel up to initial portion of airway. Thus when the resistance at 5 Hz frequency is measured, it measures total airway resistance. If there is obstruction in the airway resistance at 5 Hz is increased. Reactance is the measurement of elasticity and inertia of airways. It is denoted by X. Resonant frequency indicates frequency at which capacitative and inertive forces are equal. Various researchers have tried to find normal reference values for different age groups. Many researchers have shown that impulse oscillometry parameters are helpful in identifying increase airway resistance and reversibility of the resistance after bronchodilation. Comparative studies between spirometry and impulse oscillometry system have established that impulse oscillometry system can be used to assess the reversibility after bronchodilation. Few of the studies have agreed that impulse oscillometry system is more sensitive than spirometry. The impulse oscillometry system has been compared with body plethysmography, interruptor technique and found to give similar results with good repeatability and acceptability. In the study by Konstantinou et al the change in R5 values before and after bronchodilation -20.5% had a sensitivity of 70% and specificity of 76%. This was a study conducted which clearly showed the

usefulness of impulse oscillometry to assess lung function in preschool children.

Chapter 4: The different pulmonary function tests are described. The tests which are available are tidal breathing, thoraco-abdominal motion analysis, interruptor technique, the impulse oscillometry technique, inert gas washout technique, body plethysmography and exhaled fractional concentration of nitric oxide. Impulse oscillometry system consists of the computer generated signal which is delivered as sound wave by a loudspeaker via a pneumotachometer connected to a mouth piece. A bias tube is connected from loudspeaker to pneumotachometer. A pneumotachometer is a device used to measure airflow quantitatively. The principle is lower frequencies penetrate the lung till the periphery and higher frequencies reach only up to the beginning of the lower airway. In a normal lung the R at 5 Hz is equal in all lower and higher frequencies. If there is peripheral obstruction the R at 5 Hz is increased and R at 20 Hz is not elevated.

Chapter 5: The approval of the study by ethical committee, study design, inclusion and exclusion criteria have been described. Sample size calculation was done. A total of 106 children within 3-6 years of age with history of fever, cough, cold and/or breathlessness where the diagnosis and differentiation between wheezing episode and other respiratory disorders was not obvious based on history and clinical examination were included. Children with heart disease, and children with pneumothorax, and empyema, and children ventilated previously were excluded. A predesigned validated data collection form was used. History was taken and clinical examination of the

patient was done. All the children were subjected to impulse oscillometry before and after bronchodilation. Impulse oscillometry parameters before and after bronchodilation such as R at 5 Hz, R at 20 Hz, X at 5 Hz, X at 20 Hz, resonant frequency and area of reactance were measured. All children were followed for seven days and final diagnosis was made. Diagnosis of wheezing episode was made by increased respiratory rate, presence of bronchovesicular breathing and rhonchi. Diagnosis of pneumonia was made by respiratory rate more than 40/min, presence of crepitations on auscultation and x-ray chest suggestive of pneumonia. Impulse oscillometry was carried out as per the American thoracic society/European society's guidelines about preschool children. A playful atmosphere was maintained while performing Impulse oscillometry. Quality control was maintained as per ATS/ERS criteria.

Chapter 6: The results and discussion are described in this chapter. The total children in the study were 106. Five children did not perform the impulse oscillometry properly hence they were excluded. Out of 101 patients 18 children were excluded as they did not complete the follow up. Hence analysis of 83 children was done. The demographic parameters analyzed were age, sex. The anthropometric characters analyzed were weight and height. The symptoms analyzed were cough, cold, fever and breathlessness. The clinical parameters analyzed were respiratory rate, heart rate, rhonchi and crepts. The impulse oscillometry characters analyzed were R at 5 Hz, R at 20 Hz, X at 5 Hz, X at 20 Hz, resonant frequency (res freq) and area of reactance (AX). The x-ray chest was

done where it was felt necessary. The x-ray chest findings were compared to final diagnosis.

6.15 Impulse oscillometry parameters and final diagnosis

Table 6.23: IOS Parameters in Wheezing Episode and pneumonia.

IOS Parameter	Wheezing episode N=36	Pneumonia N=39	P-value
	Mean (95% CI)	Mean (95% CI)	
Before Nebulization R at 5 Hz	1.23 (1.20, 1.26)	1.04(1.02, 1.05)	0.07256
After Nebulization R at 5 Hz	1.04 (1.01, 1.06)	1.02(1.00, 1.03)	0.9029
ΔR5 Hz (%)	0.36 (0.33, 0.37)	0.12(0.11, 0.13)	< 0.0001
Before Nebulization R at 20 Hz	0.63 (0.62, 0.65)	0.54(0.52, 0.55)	0.0677
After Nebulization R at 20 Hz	0.57 (0.55, 0.58)	0.55(0.54, 0.56)	0.9076
ΔR20 Hz (%)	0.18 (0.16, 0.19)	0.12(0.11, 0.13)	0.3785
Before Nebulization X at 5 Hz	-0.51 (-0.49, -0.55)	-0.37(-0.35,-0.38)	0.2963
After Nebulization X at 5 Hz	-0.45 (-0.43, -0.47)	-0.33(-0.32,-0.36)	0.7279
ΔX5 Hz (%)	2.84 (2.12, 3.56)	2.44(1.74, 3.14)	0.007548

Before Nebulization X at 20 Hz	-0.18 (-0.17, -0.19)	-0.086 (-0.074, -0.098)	0.008413
After Nebulization X at 20 Hz	-0.10 (-0.09, -0.11)	-0.074 (-0.072, -0.077)	0.8684
ΔX20 Hz (%)	-273.10 (-271.8, -275.12)	-244.23 (-242.2, -246.80)	0.9511
Before Nebulization Ax value	6.68 (6.21, 7.15)	4.23(4.13, 4.33)	0.09549
After Nebulization Ax value	4.61 (4.22, 5.00)	3.76(3.67, 3.87)	0.8377
ΔAX	2.84 (2.62, 3.05)	0.96(0.91, 0.99)	<0.0001
Before Nebulization Resonant Frequency	26.31(25.96,26.66)	23.29(23.15,23.44)	0.0172
After Nebulization Resonant Frequency	24.49(24.08,24.90)	22.94(22.79,23.08)	0.4734
Δ Resonant Frequency	3.26 (3.10, 3.41)	1.68(1.61, 1.74)	0.02437

From the above table it is clear that there is difference in baseline values of R at 5 Hz in wheezing episode and R at 5 Hz in pneumonia. The change in R at 5 Hz in wheezing episode is

significant and it is not significant in pneumonia cases. In the similar way change in X at 5 Hz is significant in wheezing episode but not in pneumonia. The change in parameter AX is also similarly significant between wheezing episode and pneumonia. The change in resonant frequency is also significant in wheezing episode but not in pneumonia. These differences in R at 5 Hz X at 5 Hz, Ax and resonant frequency in wheezing episode and pneumonia indicate that these parameters of impulse oscillometry can differentiate between wheezing episode and pneumonia.

Correlation of height and weight with R at 5 Hz was done as advised by ATS/ERS statement. Thus the findings can be applied to the children with height 90 to 120 cm and weight 10 kg to 25 kg. As there is negative correlation the values go on decreasing with increasing height and weight. A regression model was developed to assess the final diagnosis of wheezing episode. The accuracy of above model is 0.8676. The sensitivity of the above model is 0.8611. The specificity of the above model is 0.8750. The area under curve of the above model is 0.8715. If cutoff of change in R at 5 Hz is taken as 25% sensitivity is 66.67% and specificity is 82.98%. A scoring system was developed based on regression equation and arbitrary cutoffs based on clinical severity. The scoring system is not yet validated.

CONCLUSIONS

From the study, it can be concluded that in 3-6 year old children with respiratory problems, the clinical presentation and impulse oscillometry can differentiate between wheezing episodes and pneumonia. The model of prediction is very useful and can predict wheezing episodes up to accuracy of 86.76% with sensitivity of 86.11% and specificity of 87.50%. Also the area under curve of the model is 0.8715. The scoring system may be helpful in diagnosis of wheezing episode but it needs validation.

LIMITATIONS

In this study, patients visiting D. Y. Patil hospital and research centre were recruited in the study. Hence it can lead to selection bias. Three to six year old children sometimes may not cooperate to do impulse oscillometry. No local reference values are available for impulse oscillometry. Hence, values given by the manufacturers were used.

RECOMMENDATIONS

Objective pulmonary function tests should be used to diagnose the wheezing episodes in children. Impulse oscillometry is an easy, child-friendly pulmonary function test which can be performed in outpatient department. Differentiation of wheezing

episode from pneumonia will help in proper management of both the conditions.

Future trends: As the respiratory diseases in children are getting diverse diagnoses, there is need to follow each and every patient individually so as to make a proper diagnosis and management. Hence, further research is needed in developing simple techniques which can be used in community or small hospital settings which will be helpful in accurate diagnosis and management.

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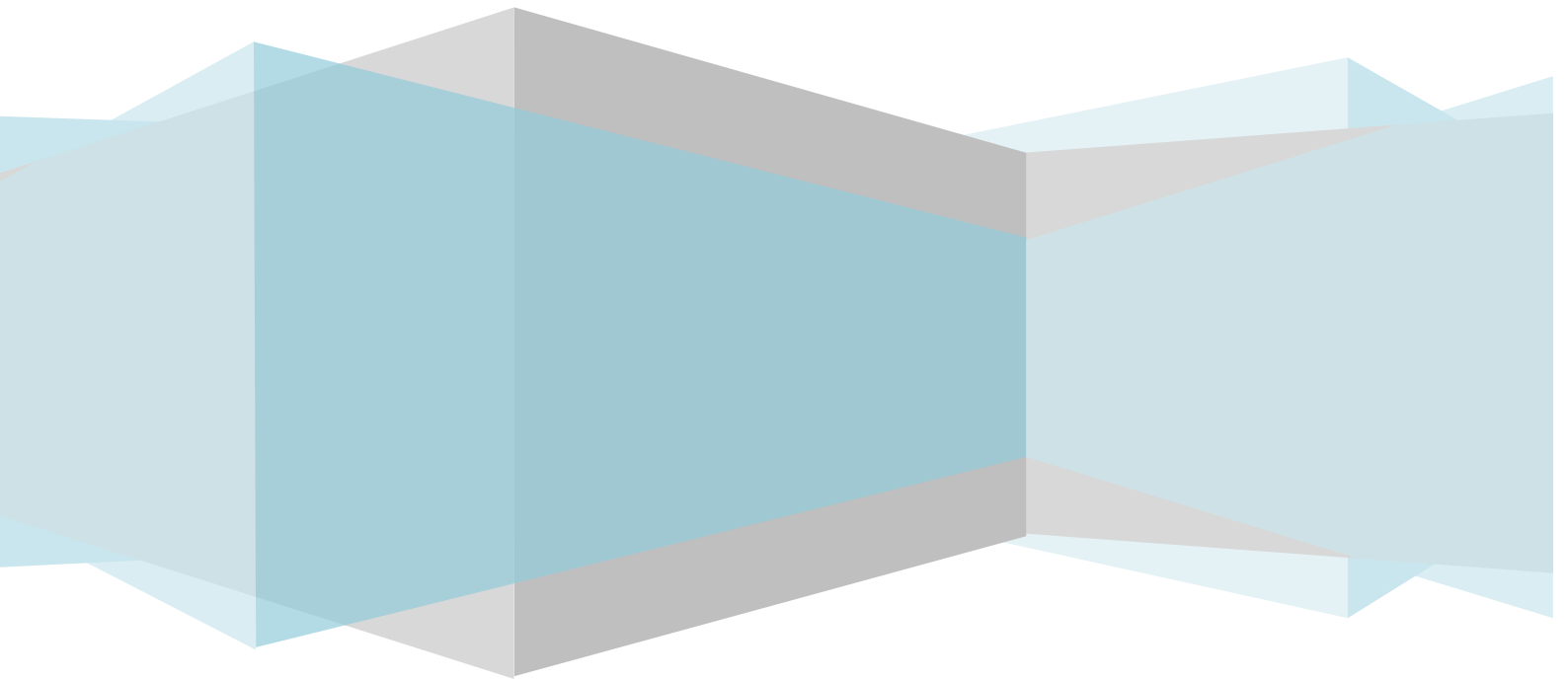

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ANNEXURE

ANNEXURE-I

PROFORMA

Clinical Presentation and Impulse Oscillometry to differentiate between Wheezing episode and Pneumonia in Children

Name
Date

Reg NO
Age/Sex

Address
Date of Birth

Anthropometry: weight height

Complaints of:

1) Cough: Nil/mild/mod/severe

2) Cold: yes/No Nasal block/Watery Discharge

3) Fever: Nil/ mild/moderate/severe

4) Breathlessness: Nil/mild/moderate/severe

Past history: rash in infancy, wheezing, nasal watery discharge, nasal block, admission for respiratory problem/food allergy

Environmental History: exposure to cold air/dampness in the wall/exposure to smoke/pet animal/

Family history: atopic dermatitis, bronchial asthma, allergic rhinitis, tuberculosis

Natal history: normal, LSCS, premature, full term, meconium aspiration

ENT exam
sinuses:

General examination:

Level of consciousness: alert

Respiration: rate dyspnea

HR BP pallor
cyanosis Lymphadenopathy

Systemic exam

Respiratory system:

Inspection: shape of chest visible veins
Kypho scoliosis

Position of trachea Intercostal indrawing

Palpation:

Tactile vocal fremitus apex beat

Percussion: Infraclavicular Mammary
Inframammary

Axillary infra axillary
Interscapular infrascapular

Auscultation: breathe sounds and adventitious sounds

Infraclavicular mammary
Inframammary

Axillary Infra axillary
Inter scapular Infrascapular

CVS:

Heart sounds Murmur

Per Abdomen: soft distended peristalsis
Hepatomegaly splenomegaly

CNS:

Level of consciousness speech
Cranial nerves

Motor system Sensory system
involuntary movement's Cerebellar signs
Gait Meningeal signs

Provisional diagnosis:

Investigations:

Hb CBC platelets

CXR
PEFR **PFT**

IOS: no.

Final Diagnosis:

ANNEXURE-II

INFORMED CONSENT FORM

I,Mr/Mrs/Ms.....Gender.....
Age.....

Residing at
.....d
o hereby confirm that:

I. I have been asked by the student /researcher of D Y Patil Medical College, hospital and Research Centre, Kolhapur ("the Medical College") whether I wish that my son/daughter to participate in a study (research) under the aegis of the Medical College.
II. Clinical Presentation and Impulse Oscillometry to differentiate between Wheezing episode and Pneumonia in Children
III. Study conducted from December 2016 on wards.
IV. Any alternate procedure or treatment should be informed
V. The nature of the study being undertaken by the student/ researcher ,as well as the extent of my son/daughter participation in it , have been duly explained to me in a language that I understand ;
VI. The potential risk and consequences associated with this study have also been duly explained to me in a language that I understand;
VII. I also understand that my son/daughter's participation in this study is only for the benefit of advancement in the field of medical research and that at no point in time is my participation being solicited for any pecuniary gain by the researcher or the Medical College;
VIII. I have also been explained that I am in no way obliged to participate in the study and that ,once I have agreed to participate in the study , I am still free to withdraw from participation in the study at any point in time upon notifying the Medical College in writing in the prescribed form without assigning any reason;
IX. There will be no financial transition between myself, the researcher and /or the D Y Patil Medical College for my participation in that study;
X. I have been explained that any data collected out of my son/daughter's participation in the study will only be used for academic purposes and /or for further medical research;
XI. I have also been reassured that any publication of the data collected during the course of the study or any publication of conclusions , shall be done on a 'no name use 'basis and shall under no circumstances reveal my son /daughter's personal identity in any personal details

likely to reveal my son/daughter's personal identity shall at all times remain confidential.

XII. I understand that if any accident or undesirable medical complication arises out of a procedure or treatment done solely for the purpose of research, my son/daughter, will be offered treatment, free of cost, by the researcher.

By affixing my signature / thumb print here to; I am therefore freely and voluntarily signifying my consent, intent and willingness to participate in the study of the student researcher for the purposes of the postgraduate dissertation under the egis of the Medical College. I also certify that my right to privacy has not been infringed in any manner.

{SIGNATURE / THUMB PRINT OF PARENT}
DATE:
WITNESSED BY:

1)NAME: **TITLE /CAPACITY :** **SIGNATURE :**		**2)NAME:** **TITLE /CAPACITY :** **SIGNATURE**

Name of Project investigator:

Address: Contact Number:

Signature of investigator:

Address: Contact Number:

Signature of investigator:

Helpline Numbers:

Contact Details of Member Secretary:

Institutional Ethics Committee:

रूग्ण संमती पत्र

डॉ. डी वाय. पाटील मेडीकल कॉलेज आपण डॉ.डी.वाय पाटील हॉस्पिटल व रिसर्च इन्स्टिट्यूट, कोल्हापूर

मी.श्री./सौ./कु/श्रीमती ..... लिंग.....

...वय..... राहणार.....

..... या पत्राद्वारे खात्री देते/देतो की,

१.मला डी.वाय.पाटील मेडीकल कॉलेजच्या द मेडीकल कॉलेज वैद्यकीय डॉक्टर संशोधक यांच्याकडून विचारले गेले की, मेडिकल कॉलेजच्या सहकार्याखाली संशोधन अभ्यासात माझ्या मुलाला अथवा मुलीला भाग घेऊ देण्याची इच्छा आहे का?

२.वैद्यकिय डॉक्टर संशोधक यांच्याकडून केल्या जाणाऱ्या संशोधन अभ्यासाचे स्वरूप व त्यामध्ये माझ्या सहभागाचा कालावधी या विषयी व्यवस्थितपणे मला सजमणाऱ्या भाषेत सांगितले आहे.

३.संशोधन अभ्यासा दरम्यान उद्भवणारे धोके आणि त्यांचे परिणाम मला समजावून व समजणाऱ्या भाषेत सांगितले आहेत.

४.मला हे सुध्दा माहित आहे की, माझ्या मुलाला अथवा मुलीला भाग घेऊ देण्याची अभ्यासातील सहभाग हा फक्त वैद्यकिय संशोधन क्षेत्राच्या प्रगतीकरिता फायदा होण्यासाठी आहे, ना की मेडिकल कॉलेज किंवा संशोधन कर्त्याकडून पैश्याच्या फायद्याकरिता.

५.मला याची पण कल्पना दिली आहे की, मी कोणत्याही स्थितीत सहभागासाठी बांधील नाही आणि एकदा मी अभ्यासात सहभागासाठी सहमती दिली तरी मी माझा अभ्यासातील सहभाग कोणत्याही वेळी विहित नमुन्यात मेडिकल कॉलेज ला लेखी अर्ज करून कोणतेही कारण न देता रद्द करू शकतो.

६.माझ्यामध्ये आणि संशोधनकर्ते आणि किंवा डी.वाय.पाटील मेडिकल कॉलेज यांच्यात अभ्यासात सहभागासाठी कोणताही आर्थिक व्यवहार असणार नाही.

७.मला याची पण कल्पना दिली आहे की, माझ्या मुलाला अथवा मुलीला भाग घेऊ देण्याची अभ्यासातील सहभागातून जी काही माहिती गोळा केली जाईल त्याचा वापर फक्त शैक्षणिक हेतू आणि किंवा पुढील वैद्यकिय संशोधनाकरिताच होईल.

८.मला याची पण खात्री दिली आहे की, अभ्यासाच्या काळात गोळा केलेल्या माहितीचे सार्वजनिक प्रसारण किंवा त्यांचा परिणामांचे सार्वजनिक प्रसारण नाव न जाहिर करता केले जाईल. कोणत्याही परिस्थितीत माझ्या मुलाला अथवा मुलीला भाग घेऊ देण्याची ओळख दाखवली जाणार नाही. कोणतीही वैयक्तिक माहिती माझ्या मुलाची अथवा मुलीची वैयक्तिक ओळख दाखवण्याची शक्यता असेल तर नेहमीच गुप्त राखली जाईल.

९.मला माहित आहे की, संशोधनाच्या हेतूकरिता केला जाणाऱ्या एखाद्या उपचार किंवा तपासणीमधून जर एखादा अपघात किंवा काही अनपेक्षित वैद्यकिय गुंतागुंत निर्माण झाली तर, वैद्यकिय संशोधक यांच्या कडुन त्यावर मोफत उपचार करण्यात येईल.

१०.या समंती पत्रातील मजकूर आणि त्याचा परिणाम मला समजणाऱ्या भाषेत व्यवस्थित समजावून सांगितलं आहे.

रूग्णाचे पालक

नाव व पत्ता साक्षीदार

....

....

....

ANNEXURE-III

ETHICAL COMMITTEE APPROVAL LETTER

D. Y. PATIL MEDICAL COLLEGE, KOLHAPUR
Constituent College of D.Y.Patil Education Society Deemed University, Kolhapur
NAAC Accredited 'A' Grade

Dr. Rakesh Kumar Sharma
Dean & Professor (Obst. & Gyn.)

Padmshree Dr. D. Y. Patil
Founder President

Dr. Sanjay D. Patil
President

Outward No. DMCK/...../20

Date :

INSTITUTIONAL ETHICS COMMITTEE, D. Y. PATIL MEDICAL COLLEGE, KOLHAPUR.

2016/ 43/PA- Ph. D

Date: 19 SEP 2016

This is to certify that the research project titled

"Clinical evaluation of respiratory problems in children and its correlation with impulse oscillometry."

Submitted by : **Dr. Suhas Kulkarni**

Under the supervision of appointed Guide (if any): **Dr. Anil B. Kurane**

Has been studied by the Institutional Ethics Committee (IEC) at its meeting held on 09/09/2016 and the student has been granted approval for the study with due effect with the following caveats:

1. If you desire any change in the protocol or standard recording document at any time, please submit the same to the IEC for information and approval before the change is implemented.
2. All serious and/or unexpected adverse events due to the drug/procedures tested in the study must be informed to the IEC within 24 hours and steps for appropriate treatment must be immediately instituted.
3. In case of injury/disability/death of any participant attributable to the drug/procedure under study, all compensation is to be made by the sponsor of the study.
4. The Chief investigator/Researcher must inform the IEC immediately if the study is terminated earlier than planned with the reasons for the same.
5. The final results of the study must be communicated to the IEC within 3 months of the completion of data collection.
6. The researcher must take all precautions to safeguard the rights, safety, dignity and wellbeing of the participants in the study.
7. The researcher must be up to date about all information regarding the risk/benefit ratio of any drug/procedure being used and any new information must be conveyed to the IEC immediately. The IEC reserves the right to change a decision on the project in the light of any new knowledge.
8. Before publishing the results of the study, the researcher must take permission from the Dean of the Institution.
9. The approval is for the Period of 24 months from date of meeting of Institutional Ethics Committee.

Dr. Mrs. Shimpa R. Sharma
(Member Secretary, IEC)

Dr. Mrs. Vasanti Rasam
(Act. Chairperson)

869, 'E' Kasaba Bavada, Kolhapur-416 006 (MS) INDIA. Phone No. : (0231) 2601235-36, Fax : (0231) 2601238,
Web: dypatilmedicalkop.org. E-mail : dypatilmedicalcollege@gmail.com

MASTER CHART

Sr.No.	PATIENT NAME	AGE	SEX	HT	WT	ADDRESS	DATE	DOB	COMPLAINTS	cough	cold	fever	Breathlessnes	HR	RR	RS	SPO2	HB	PCV	PLATE	WBC	ESR	CXR REPORTS
1	GUNJAN JIVITRAMANI	3	F	96	15.6	GANDHINAGAR	4/12/2016	8/30/2012	COUGH 8 DAYS	2	1	1	3	144/MIN	48/MIN	RHONCHI++	98%						
2	TANISHKA SAPATE	5	M	116	25	HUPARI	4/15/2016	9/22/2010	COUGH,COLD,BREATHLESSNESS,FEVER 3DAYS	3	2	2	2	124/MIN	38/MIN	CREPTS	98%						
3	RUDRA CHOUGULE	3	M	94	12.2	SAUNDALAGA	7/8/2017	3/20/2014	COUGH, FEVER	4	1	1	1	112/MIN	36/MIN	CREPTS+	95%						
4	KANISHKA KADAM	3	F	101	14.9	LAXMI NAGAR	7/20/2017	8/30/2013	COLD,COUGH,BREATHLESSNESS 3 DAYS	3	1	1	3	116/MIN	42/MIN	RHONCHI++	96%						
6	SHARAYU DARBHE	4	F	112	20.8	KOLHAPUR	7/29/2017	3/28/2013	COUGH AT NIGHT	3	1	1	1	126/MIN	40/MIN	RHONCHI+	98%						
7	DHRUVRAJ GURAV	5	M	106	14.2	GUDEWADI	9/1/2017	11/24/2012	COLD, COUGH, FEVER	2	2	2	2	140/MIN	41/MIN	RHONCHI+	97%						
8	SAI KAMBALE	4	F	104	14.4	MUDSHINGI	9/14/2017	8/28/2013	FEVER,COUGH,NASAL BLOCK 3 DAYS	2	3	2	2	138/MIN	42/MIN	RHONCHI+	98%						
9	JOAANA BENEDICT	3	F	100	13.64	TARABAI PARK	9/15/2017	5/23/2014	COUGH VARIANT ASTHMA	2	1	1	2	130/MIN	42/MIN	CLEAR	97%						
10	SHREYASH JADHAV	3	M	92	11.7	SHIROLI	9/15/2017	1/2/2014	FEVER HIGH GRADE, COUGH 2 DAYS	4	3	4	2	108/MIN	40/MIN	CREPTS+ RHONCHI++	96%						
11	TANMAYEE MEDHE	4	F	97	12.92	KOLHAPUR	9/18/2017	8/26/2013	COUGH,COLD,BREATHLESSNESS 2 DAYS	2	1	2	2	128/MIN	44/MIN	RHONCHI++	96%						
12	AARADHYA VHARAMBALE	5	F	111	16	VARANAGE PADALI	9/30/2017	4/11/2012	COUGH ,FEVER, BREATHLESSNESS 4 DAYS	4	1	4	4	130/MIN	48/MIN	RHONCHI+	95%						
13	ABDULMAZID KOTVAL	3	M	102	16.44	MUKTA SAINIK	11/10/2017	11/7/2014	COUGH, BREATHLESSNESS, FEVER 4 DAYS	2	1	2	2	108/MIN	40/MIN	RHONCHI++	95%						
15	SAIRAJ PADWAL	5	M	104	15	PADAWALWADI	1/9/2018	12/24/2012	COUGH, COLD, FEVER 3 DAYS	4	1	3	4	96/MIN	48/MIN	RHONCHI++	97%						
16	AARADHYA GHOLAPE	4	F	100	15	KOLHAPUR	2/1/2018	3/22/2013	COUGH 8 DAYS	2	1	1	1	122/MIN	40/MIN	RHONCHI++	96%						
17	VIRAJ INGROLE	3	M	105	16.42	HUPARI	1/16/2018	5/16/2014	COUGH,COLD,BREATHLESSNESS 10DAYS	2	3	1	2	86/MIN	40/MIN	CLEAR	97%						
18	TANISHKA JOSHI	5	F	108	14.45	SANGALI	5/9/2017	8/26/2012	FEVER. COUGH	2	1	2	2	104/MIN	36/MIN	CREPTS+	96%						
19	SAMARTHA PATIL	4	M	105	14	UCHGAON	3/11/2016	10/13/2011	COUGH AT NIGHT 3 DAYS	3	2	1	1	88/MIN	36/MIN	CREPTS+	98%						
20	ALFIM MULLA	3	F	96	15	KAWALANAKA	8/31/2016	10/16/2012	COUGH,COLD,5 DAYS	2	1	1	3	152/MIN	40/MIN	RHONCHI+	95%						
21	VARAD MALI	4	M	101	15	UCHGAON	9/5/2016	11/1/2011	FEVER, COUGH, BREATHLESSNESS	3	1	2	3	125/MIN	40/MIN	CREPTS+	95%						
22	SHRIRAJ PATIL	3	M	97	12.5	SHIRALA	2/28/2017	3/2/2014	COUGH AT EARLY MORNING SINCE 1 MONTH	3	1	1	2	108/MIN	36/MIN	CLEAR	96%						
23	NAKSHATRA DESAI	4	F	98	14.18	NAGAON	3/1/2017	2/23/2013	COUGH SINCE 1 MONTH, COLD	4	1	2	1	100/MIN	28/MIN	CLEAR	98%						NORMAL
24	ATHARV FADATARE	5	M	120	23	MAJGAON	12/29/2016	2/22/2011	COUGH	3	1	1	2	92/MIN	28/MIN	CREPTS+	98%						
25	FARAJ MULLANI	4	M	96	12	KADAMWADI	12/7/2016	8/23/2012	FEVER,COUGH,COLD SINCE8 DAYS	2	1	2	3	120/MIN	42/MIN	RHONCHI+	96%						
26	ANAY BADE	4	M	107	16.1	NIGADEADI	3/2/2018	10/7/2013	COUGH 2 MONTH	3	1	1	1	86/MIN	40/MIN	RHONCHI+	96%						
27	ADITYA JAGTAP	5	M	112	18.1	UHAGAV	3/13/2018	3/9/2013	COUUGH 5 COLD 4 DAYS	2	1	1	1	112/MIN	36/MIN	CREPTS	96%						
28	INAYA BALEKHAN	5	F	115	17.88	VIKRAMNAGAR	4/9/2018	2-Oct	COUGH 3 WEEKS	2	1	1	1	108/MIN	34/MIN	CLEAR	96%						
30	GIRIJA KAMBALE	4	F	91	11.12	YALGUD	7/14/2018	6/26/2014	COLD COUGH 5 DAYS	3	3	3	3	136/MIN	42/MIN	CREPTS	98%	9.6	31	370000	7400	27	NORMAL
31	TANAYA DIGE	4	F	97	11.8	RUKADI	7/21/2018	8/28/2013	FEVER LOW GRADE COUGH COLD 2 DAYS	3	1	3	3	108/MIN	42/MIN	CREPTS	96%	9.9	32	392000	7100	25	NORMAL
32	SIDHI BENAKE	4	F	96	12	DARYACHE VADA.	7/21/2018	3/2/2014	WHEEZING EPISODE VIRUS INDICATES	3	1	1	3	88/MIN	44/MIN	RHONCHI	99%	11.1	31	419000	7700	15	PNEUMONIA
33	CHINMAY KULKARNI	5	M	115	19	PETH VADGAV	8/2/2018	10/15/2012	COUGH FEVER NASAL DISCHA.	3	1	1	3	92/MIN	24/MIN	CREPTS	98%	NO					PNEUMONIA
34	OM KURHADE	4	M	101	13.73	DEVKAE PANAND	8/9/2018	8/22/2013	3 WKEES COUGH ON OFF FEVER MILD	3	1	2	1	96/MIN	36/MIN	CREPTS	98%	11.2	32	333000	11400	23	NORMAL
35	SHREYASH KOLCHALMI	3	M	102	14.87	JADHAV WADI	8/21/2018	1/1/2015	COLD COUGH 5 DAYS	2	1	1	1	106/MIN	40/MIN	RHONCHI	96%	11.5	33	300000	7800	14	WHEEZING EPISODE
36	YASHARAJ KAMBALE	5	M	106	17.1	PUNGAV	8/21/2018	10/22/2012	FEVER COUGH 8 DAYS	3	3	3	3	96/MIN	40/MIN	CREPTS+	96%	10.4	32	338000	8300	24	PNEUMONIA
37	SIDHARTH KUMBHAR	3	M	97	13	WARNANAGAR	9/3/2018	5/2/2015	COUGH GRUINTING MILD FEVER 2 DAYS	4	1	2	2	136/MIN	44/MIN	RHONCHI	94%	103	31	221000	10800	22	PNEUMONIA
38	JANAVHI LAMBORE	5	F	104	14.2	GAGANBAWADA	9/22/2018	8/10/2013	BRETHLESSNISS 2 DAYS	3	3	3	3	144/MIN	60/MIN	RHOCHI++	87%	10.2	31	353000	9300	25	NORMAL
39	ARADHYA AADSULE	3	F	101	12.8	GADHINAGAR	10/4/2018	10/25/2015	BREATHLESS GR.1 FEVER COLD COUGH 4 DAYS	4	1	3	3	112/MIN	38/MIN	CREPTS	98%	10.9	33	197000	5800	23	PNEUMONIA
41	JIKRA MULLA	5	F	106	15	BAWADA	10/5/2018	8/23/2013	COUGH COLD AT NIGHT GRA.3	3	1	1	2	110/MIN	24/MIN	CLEAR	96%	NO					PNEUMONIA
43	SHRAVNI HADAPAD	3	F	92	11.9	GADHINAGAR	10/10/2018	4/6/2015	COLD COUGH GRADE 2	3	1	4	1	160/MIN	34/MIN	CREPTS	96%	7.5	28	297000	16500	30	PNEUMONIA
44	ANOSH M GAIKWAD	4	M	107	16.7	NAGALA PARK	10/24/2018	3/10/2014	COUGH COLD	3	1	1	3	118/MIN	44/MIN	RHOCHI++	96%	NO					NO
45	SWARANJALI PATIL	3	F	94	13.8	SHIROLI	10/8/2018	9/12/2015	COUGH COLD	3	1	1	2	108/MIN	36/MIN	CREPTS	96%	NO					NO
47	PRITHVIRAJ PALKAR	5	M	109	16.3	PATOLEWADI	1/8/2019	11/21/2013	COUGH ON & off 2 months	4	1	1	3	102/min	42/MIN	RHONCHI	94%	12	35	421000	10400	15	PNEUMONIA
48	KIRAN PHAPE	3	M	100	15.2	KADAMWADI	1/8/2019	12/26/2015	COUGH	3	1	2	1	110/MIN	32/MIN	CLEAR	96%	10.5	32	401000	9100	24	NORMAL
49	PURVA YELVANKAR	3	F	96	11.5	SIDHARTH NAGAR	1/17/2019	2/17/2015	COUGH ,COLD 2 DAYS	2	1	3	2	96/MIN	48/MIN	RHONCHI+	98%	11.1	36	542000	13500	13	PNEUMONIA
50	ANJALI JADHAV	4	F	104	15.9	KASABA BAWADA	1/29/2019	9/11/2014	COUGH ON & OFF 2 MONTH	3	1	1	1	108/MIN	26/MIN	CLEAR	98%	10.7	33	465000	11300	22	NORMAL
51	ARCHIS HATTRAGI	5	M	106	16.1	LIC COLONY	1/30/2019	5/8/2014	COUGH	4	2	1	3	132/MIN	40/MIN	RHONCHI++	96%	10.9	33	563000	9400	21	PNEUMONIA
52	PRATIKSHA BANHATTI	5	F	100	11.3	MUDASHINGI	2/16/2019	4/30/2013	COUGH 2-3 DAYS	3	1	2	3	118/MIN	46/min	RHONCHI	97%	12	37	414000	10000	17	PNEUMONIA
53	PRANJAL JADHAV	5	F	100	13.4	HUPARI	4/5/2019	9/28/2014	COUGH 2 MONTH	3	1	1	1	104/MIN	24/MIN	CLEAR	96%	11.4	32	380000	7000	26	NORMAL
54	KISHAN ZAREKARI	4	M	101	15.9	LONAD	4/11/2019	11/11/2014	COUGH COLD	2	1	2	1	96/MIN	24/MIN	CREPTS	96%	12.2	32	254000	7300	21	PNEUMONIA
55	NANDINI WADKAR	4	F	92	11.6	BHOSALE WADI	4/24/2019	4/7/2015	COUGH 2 MONTH	3	1	1	1	112/MIN	36/MIN	CLEAR	97%	11.9	32	355000	8300	21	PNEUMONIA
57	ABDULSAMAD CHIKODE	6	M	109	16.7	KADAMWADI	7/25/2019	9/10/2013	COUGH	2	1	2	1	112/MIN	36/MIN	CLEAR	96%	12.9	40	420000	8900	17	NORMAL
58	PURVI KAMBALE	3	F	97	11.2	KADAMWADI	7/29/2019	1/24/2016	COUGH 2 DAYS	3	2	1	1	136/MIN	36/MIN	RHONCHI+	93%	NO					NO
59	ANAND SAMANT	6	M	101	16.7	JADHAVWADI	8/29/2019	4/23/2014	COUGH 2 DAYS	2	2	1	1	136/MIN	42/MIN	RHONCHI+	94%	10.8	36	467000	10100	20	PNEUMONIA
60	RUGVED SHINDE	4	M	99	17	SALAVAN	8/29/2019	9/20/2015	COUGH 2 DAYS	4	2	2	1	108MIN	36/MIN	CREPTS	94%	9.6	30	248000	8100	23	NORMAL
61	AVANISH PATIL	4	M	92	16.8	JADHAVWADI	8/29/2019	6/28/2016	COUGH	3	2	1	1	128/MIN	32/MIN	RHONCHI	98%	NO					PNEUMONIA
62	LUBDHA BHAGAVAT	4	F	101	15.1	KARENDE MALLA	8/29/2019	12/31/2014	COUGH	3	1	1	1	130/MIN	36/MIN	CLEAR	96%	NO					PNEUMONIA
64	PRADHNYA SHENDE(DY)	4	F	87	12.3	AAJARA	9/17/2019	8/16/2015	COUGH	4	1	1	2	96/MIN	40/MIN	RHONCHI+	96%	NO					NO
66	SHIVAM KAMBALE	3	M	94	13.6	KADAMWADI	9/17/2019	10/5/2015	COUGH,COLD,FEVER	4	2	3	3	137/MIN	46/MIN	RHONCHI	94%	9.6	33	441000	9600	23	PNEUMONIA
67	AALIYA AAGA	5	F	97	14.2	PANHALA	9/17/2019	8/1/2014	COUGH,COLD,FEVER	3	2	2	2	120/MIN	38/MIN	RHONCHI	96%	11.4	36	506000	12800	15	NORMAL
69	UZER BAGAVAN	4	M	104	14.7	UNIK PARK	9/20/2019	2/5/2015	COUGH 6 DAYS	3	2	4	1	116/MIN	32/MIN	CLEAR	96%	12.9	39	135000	4100	26	PNEUMONIA
71	JAKI DESAI	5	M	111	16.8	SHIROLI	10/1/2019	5/5/2014	COUGH FEVER 4 DAYS	2	2	3	1	154/MIN	36/MIN	RHONCHI+ CREPT	98%	11.2	33	318000	4300	17	PNEUMONIA
72	ABHIRAJ BHOSALE	5	M	106	18.8	WALIVADE	10/1/2019	11/4/2013	COUGH	4	1	1	2	98/MIN	44/MIN	RHONCHI	96%	9.3	34	240000	6100	26	NORMAL
73	AMEY DOLARE	6	M	106	17.4	SHIROLI	10/1/2019	12/7/2013	COUGH	4	1	1	2	92/MIN	48/MIN	RHONCHI	96%	11.8	37	570000	10300	25	PNEUMONIA
74	SALONI KADAM	4	F	101	12.7	KADAMWADI	10/4/2019	12/15/2015	COUGH	2	1	1	1	118/MIN	38/MIN	CLEAR	98%	12.1	36	326000	12900	15	PNEUMONIA
77	AARADHANA AADAV	3	F	99	14.4	MUKT SAINIK	10/5/2019	10/12/2015	COUGH ,COLD,FEVER,BRATHLESSNESS	3	1	3	3	128/MIN	48/MIN	RHONCHI	98%	12	38	389000	11000	15	NORMAL
78	SHRAVAN KAMBALE	3	M	97	13.36	VICHARE MALL	10/15/2019	6/25/2016	COUGH,COLD,	3	1	1	1	88/MIN	28/MIN	CLEAR	98%	10.8	33	352000	10900	24	FB
79	RECHEL GOLAPALLI	3	F	92	11.72	VIKRAM NAGAR	10/15/2019	9/13/2016	COUGH,COLD	3	1	1	1	96/MIN	32/MIN	CLEAR	96%	11.4	37	256000	5600	15	PNEUMONIA
81	AAYUSH MEKERI	5	M	111	16.29	MUDASHINGI	10/28/2019	11/14/2014	COUGH	4	1	1	1	138/MIN	30/MIN	CREPTS	96%	13.6	36	426000	12600	24	PNEUMONIA
82	FOUZIA MULLA	5	F	106	17.42	UJALAI WADI	11/21/2019	3/21/2014	COUGH	2	1	1	1	92/MIN	28/MIN	CLEAR	98%	13	38	342000	9700	22	NORMAL
83	ADVAIT PATIL	4	M	104	18.28	KADAMWADI	12/9/2019	10/28/2015	COUGH	2	1	1	3	108/MIN	42/MIN	RHONCHI	98%	10.1	34	188000	5000	23	PNEUMONIA
84	RAJVEER DESAI	3	M	99	15.3	BAPAT CAMP	12/14/2019	7/17/2016	COUGH COLD FEVER	3	1	2	3	116/MIN	46/MIN	RHONCHI	96%	12.1	35	289000	5500	25	PNEUMONIA
85	DAKSH VARAPE	5	M	112	19.8	SHIVAJI PARK	12/16/2019	9/23/2014	COUGH	3	1	1	1	104/MIN	30/MIN	CLEAR	96%	12	36	290000	8000	21	NORMAL
86	DRUSHTI VARAPE	5	F	104	16.4	SHIVAJI PARK	12/16/2019	9/23/2014	COUGH	2	1	1	1	104MIN	28/MN	CLEAR	96%	10.6	34	268000	8300	22	PNEUMONIA
87	AARAV INGAVALE	3	M	91	11.3	WARANA KODOLI	12/20/2019	8/24/2016	COUGH	4	1	3	2	96/MIN	40/MIN	CREPTS	96%	12	38	204000	9800	13	NORMAL
89	ATHARV WAGHAMARE	3	M	99	13.4	MANER MALL	12/22/2019	11/24/2016	COUGH,COLD ,FEVER	4	1	3	1	122/MIN	36/MIN	RHONCHI	96%	11.4	39	418000	11100	22	NORMAL
90	AAROHI TIRALE	3	F	99	14.9	KAGAL	12/24/2019	4/6/2016	COUGH,COLD, FEVER,BRATHLESSNESS	2	2	2	2	110/MIN	32/MIN	CREPTS	98%	NO					PNEUMONIA
91	SAMRATH PATIL	3	M	94	12.9	KADAMWADI	12/24/2019	4/28/2016	COUGH,COLD,	4	1	1	2	88/MIN	34/MIN	CLEAR	96%	12.2	38	321000	9300	14	NORMAL
92	MUSTAFA SHAIKH	4	M	104	14.27	TENBLAIWADI	1/4/2020	12/8/2015	COUGH,COLD,FEVER	3	1	3	2	122/MIN	36/MIN	CREPTS	98%	8.8	32	438000	9300	29	PNEUMONIA
93	ANSAR MOKASHI	3	M	94	12	POHALE WADI	1/2/2020	7/27/2016	COUGH,COLD	4	1	1	2	98/MIN	34/MIN	CLEAR	98%	12.2	37	509000	8800	13	NORMAL
94	NIHAR KOLI	4	M	96	13.3	DEVGAD	2/1/2020	12/2/2015	COUGH,COLD,FEVER	4	2	2	2	102/MIN	30/MIN	CLEAR	98%	11.6	34	290000	6900	14	NORMAL
96	SWARAJ CHAVAN	5	M	94	12.7	SHIYE	2/3/2020	11/20/2015	COUGH,FEVER	4	1	4	1	98/MIN	36/MIN	CREPTS	95%	10.7	32	372000	7700	22	PNEUMONIA
97	SARTH MASKE	5	M	107	16.33	MAHADIK COLONY	2/6/2020	2/8/2015	COUGH,COLD	4	1	1	1	108/MIN	42/MIN	CREPTS	96%	NO					PNEUMONIA
98	SALONI YADAV	5	F	110	14	SHIROLI	3/5/2020	9/17/2014	COUGH,COLD,FEVER	3	1	2	1	132/MIN	44/MIN	RHONCHI+	93%	12.9	40	266000	10500	20	NORMAL
101	UMAR KHATIB	4	M	104	15	HERALE	4/4/2020	3/22/2015	COUGH,BREATHLESSNESS	2	1	1	2	96/MIN	32/MIN	CREPTS	96%	NO					NORMAL

Sr.No.	Pre nebulization AX	Post nebulization AX	R AT 5 HzPredicted	pre nebulization Actual R at 5 Hz	pre nebulization R5 percentage	post nebulization R at 5 Hz actual VALUE	post nebulization R 5 percentage	post nebulization percentage change in R5	R 20 Predicted	Pre nebulization R20 actual value	pre nebulizationR 20 percentage	post nebulization R 20 actual VALUE	post nebulization R 20 percentage	post nebulization percentage change in R20	X 5 Predicted	pre nebulization X5 ACT.VAL.	Pre nebulization X 5 percentage	post nebulization ACT.VAL X at 5 Hz	post nebulization percentageX at5 Hz	pre &post nebulization percentage changeX at 5	X AT 20 HZ Predicted	Pre Nebulization actual valueX AT 20	X at 20 Pre nebulization percentage	post nebulization X AT 20 HZ	percentage changeX at 20 Hz	Pre nebulization RES.FREQ	post nebulization RES.FREQ	PROVISIONAL DIAGNOSIS	FINAL DIAGNOSIS
1	7.7	3.3	1.19	1.67	140.9	1.05	88.7	52.20%	0.97	0.82	84	0.65	66.8	31.80%	-0.38	-0.46	120.9	-0.16	42.8	78%	0.03	-0.22	-808.8	-0.11	-399	28.82	25.65	WHEEZING EPISODE	Wheezing episode
2	3.93	3.47	0.85	1.11	130.1	1.07	125.6	4.50%	0.66	0.52	78.8	0.61	91.8	13.00%	-0.27	-0.22	82.1	-0.18	68.3	13.80%	0.05	-0.11	-226.9	-0.11	-220.1	23.01	25.59	PNEUMONIA	pneumonia
3	3.34	3.1	1.23	1.18	95.9	1.02	83.2	12.70%	1.02	0.69	68.1	0.51	50.5	17.60%	-0.39	-0.24	61.7	-0.14	36.7	25%	0.03	-0.09	-337	-0.07	-250.3	24.6	21.6	PNEUMONIA	pneumonia
4	5.22	2.75	1.06	1.42	133.3	1.29	121.6	11.70%	0.87	0.83	95.4	0.9	103.5	8.10%	-0.34	-0.3	88.6	-0.13	39.2	49.40%	0.04	-0.17	-449.2	-0.07	-188.7	25.73	24.08	WHEEZING EPISODE	Wheezing episode
6	4.2	2.99	0.89	0.64	71.9	0.97	110	38.10%	0.75	0.42	55.9	0.38	51	4.90%	-0.28	-0.11	37.6	-0.13	46.4	8.80%	0.04	-0.02	-52.9	0.02	35.9	20.6	19.55	WHEEZING EPISODE	Wheezing episode
7	4.82	3.41	0.96	1.01	105.8	1.06	110.9	5.10%	0.79	0.47	60.2	0.7	89.3	29.10%	-0.31	-0.39	125.2	-0.3	96.1	29.10%	0.05	-0.14	-294.5	-0.11	-239.9	24.42	24.96	PNEUMONIA	pneumonia
8	1.09	4.8	1	0.64	64	1.19	119.1	55.10%	0.82	0.46	56.1	0.46	56	0.10%	-0.32	0	0.4	-0.39	121.2	120.80%	0.04	-0.04	-95.4	0.01	14.8	22.48	19.89	WHEEZING EPISODE	Wheezing episode
9	6.09	3.29	1.08	1.46	135.5	0.98	91.3	44.20%	0.89	0.48	54.3	0.51	57	2.70%	-0.35	-0.01	1.6	0.07	-21.5	23.20%	0.04	-0.16	-421.7	-0.14	-379.3	22.87	24	COUGH VARIANT ASTHMA	OTHERS
10	8.14	8.42	1.29	1.57	121.6	1.63	126.4	4.08%	1.07	0.42	39.7	0.61	57.1	17.40%	-0.41	-0.78	189.4	-0.69	166.6	22.80%	0.02	-0.11	-529	-0.22	-993.8	22.04	24.69	PNEUMONIA	pneumonia
11	6.97	5.03	1.15	1.57	137.5	1.17	102.3	35.20%	0.95	0.83	87.8	0.44	45.9	41.90%	-0.37	-0.04	11.8	-0.49	133.1	121.30%	0.03	-0.27	-828.9	0.04	114.8	31.64	19.31	PNEUMONIA	Wheezing episode
12	5.85	5.02	0.88	1.51	171	1.23	139	32%	0.72	0.44	61	0.47	106	45.00%	-0.29	-0.27	93.1	-0.51	175.8	82.76%	0.05	-0.06	-120	-0.07	-140	21.28	21.84	WHEEZING EPISODE	Wheezing episode
13	2.43	4.4	1	0.65	61.8	0.96	91.6	29.80%	0.85	0.3	35.3	0.35	41	5.70%	-0.34	-0.21	62.7	-0.52	154.5	91.8	0.04	-0.01	-19.9	0.01	38.3	20.29	21.54	BRONCHIAL ASTHMA	OTHERS
15	10.73	4.04	1	1.86	186.2	1.01	101.7	84.50%	0.82	0.69	84	0.6	73.8	10.20%	-0.32	-0.61	188.7	-0.39	120.4	68.30%	0.04	-0.33	-760.3	-0.13	-296	31.4	24.3	PNEUMONIA	Wheezing episode
16	6.2	2.82	1.09	1.29	118.7	0.97	89.4	29.30%	0.89	0.84	94.5	0.71	80.2	14.30%	-0.35	-0.56	162	-0.26	74.9	87.10%	0.04	-0.23	-633.9	-0.1	-272	28.35	25.82	WHEEZING EPISODE	Wheezing episode
17	4.5	2.37	0.99	1.03	104.5	0.77	78.3	26.20%	0.8	0.65	80.7	0.49	60.9	19.80%	-0.32	-0.36	114.5	-0.19	60.6	53.90%	0.04	-0.16	-381.1	-0.07	-152.4	26.53	23.08	COUGH VARIANT ASTHMA(wheezing episode)	OTHERS
18	3.61	3.39	0.93	0.86	93.3	0.93	100	7.30%	0.76	0.47	62.2	0.46	60	2.20%	-0.3	-0.47	154.7	-0.37	122.3	32.40%	0.05	-0.02	-45.3	-0.05	-92.3	20.72	21.54	PNEUMONIA	pneumonia
19	5.53	2.47	0.98	1.18	120.4	1.14	117.1	3.30%	0.8	0.4	50.1	0.77	95.3	45.20%	-0.32	-0.43	135.9	-0.16	51.1	84.8	0.05	-0.09	-195.9	-0.08	-166.8	21.79	24.87	pneumonia	pneumonia
20	5.56	5.87	1.09	1.4	128.4	1.3	119.6	8.80%	0.89	0.6	67.5	0.49	55.2	12.30%	-0.35	-0.35	100.6	-0.45	129.2	28.40%	0.04	-0.13	-374.3	-0.11	-312.9	22.68	22.74	WHEEZING EPISODE	OTHERS
21	1.51	1.53	1.06	0.67	63.1	0.8	75	11.90%	0.87	0.48	55.5	0.56	64.4	8.90%	-0.34	0.01	-3.2	-0.08	22.3	-25.50%	0.04	-0.05	-126.5	-0.02	-51.4	28.33	21.91	PNEUMONIA	Wheezing episode
22	4.84	4.37	1.15	1.31	114	1.11	96.9	17.50%	0.95	0.71	74.6	0.58	61.5	13.10%	-0.37	-0.47	128.4	-0.25	66.7	61.70%	0.03	-0.17	-513.6	-0.08	-253.9	26.45	25.09	RECURRENT COUGH WITH AID? COUGH VARIANT	OTHERS
23	8.61	6.34	1.15	1.72	149.8	1.53	133.4	16.40%	0.95	0.97	102.4	0.86	90.4	12.00%	-0.37	-0.62	167.7	-0.43	117.6	50.10%	0.03	-0.28	-871	-0.23	-702.9	31.93	27.42	COUGH VARIANT ASTHMA(wheezing episode)	pneumonia
24	1.51	1.42	0.8	0.71	89.5	0.83	104.5	15%	0.62	0.54	86.5	0.64	102.8	16.30%	-0.25	-0.27	107.3	-0.22	87.3	20%	0.05	0	8	0	7.1	19.69	19.69	wheezing episode	pneumonia
25	5.61	3.35	0.98	1.2	121.7	1	102.2	19.50%	0.79	0.48	61	0.58	74	13.00%	-0.31	-0.34	109	-0.31	100.7	9.70%	0.04	-0.18	-438.1	-0.09	-231.8	25.86	24.48	WHEEZING EPISODE	OTHERS
26	6.33	4.49	0.95	1.24	130.4	1.13	118.5	11.90%	0.77	0.51	65.3	0.53	68.6	3.30%	-0.31	-0.57	187.3	-0.2	65.5	121.80%	0.05	-0.14	-305.6	-0.13	-274.9	24.26	25.47	WHEEZING EPISODE	pneumonia
27	2.56	1.83	0.88	0.69	79.1	0.63	72.1	7%	0.71	0.46	65.3	0.44	61.9	3.40%	-0.28	-0.34	121.6	-0.3	105.7	15.90%	0.05	-0.06	-119.5	-0.01	-20.4	22.72	20.6	WHEEZING EPISODE	pneumonia
28	7.49	4.36	0.84	1.46	173.8	0.92	109.5	64%	0.67	0.45	67.1	0.36	53.73	13.37%	-0.27	-0.68	251.85	-0.42	155.5	96.35%	0.05	-0.15	-300	-0.09	-180	24.12	22.6	WHEEZING EPISODE	OTHERS
30	1.66	2.9	1.32	0.61	46.3	1.31	99.4	53.10%	1.1	0.48	44	0.8	73	29.00%	-0.42	-0.08	19.2	0.1	-23.1	-42.30%	0.02	-0.06	-285.9	-0.21	-1070	27.52	30.57	PNEUMONIA	pneumonia
31	3.92	4.83	1.14	1.13	98.5	1.17	102.3	3.80%	0.95	0.61	64.2	0.46	47.9	16.30%	-0.37	-0.24	65.5	-0.32	87	21.50%	0.03	-0.1	-304.8	-0.11	-336	23.16	22.97	PNEUMONIA	pneumonia
32	2.52	2.91	1.06	0.91	85.8	0.84	79.4	6.40%	0.87	0.63	72.2	0.53	61	11.20%	-0.34	-0.33	95.3	-0.26	76	19.30%	0.04	-0.04	-106.9	-0.1	-265.6	21.72	25.4	WHEEZING EPISODE	Wheezing episode
33	3.76	1.59	0.84	0.79	93.5	0.67	79.9	13.60%	0.67	0.37	55.6	0.51	76.4	20.80%	-0.27	-0.34	125.6	-0.18	66.3	59.30%	0.05	-0.1	-184	-0.04	-73	22.84	23.49	PNEUMONIA	pneumonia
34	9.59	7.3	1.06	1.86	175.7	1.59	150.3	25.40%	0.87	0.91	104.3	0.81	93.3	11.00%	-0.34	-0.52	153.4	-0.41	118.9	34.50%	0.04	-0.17	-434.3	-0.15	-391.1	25.39	24.96	WHEEZING EPISODE	pneumonia
35	2.94	1.84	1.04	0.91	87	0.98	94.5	7.50%	0.85	0.57	66.4	0.7	82.6	16.20%	-0.34	-0.3	89.3	-0.23	67.8	21.50%	0.04	-0.09	-218.5	0	-2.3	23.31	20.05	WHEEZING EPISODE	pneumonia
36	2.33	4.22	0.97	1.16	119.5	1.19	122.9	3.50%	0.79	0.98	123.9	0.85	108.3	15.60%	-0.31	-0.27	85.1	-0.36	115.7	30.60%	0.04	-0.07	-162.7	-0.12	-280.2	26.14	29.75	ALLERGIC RHINITIS WITH WHEEZING	pneumonia
37	8.23	4.42	1.15	1.7	147.8	1.26	109.8	38%	0.95	0.7	74	0.78	81.6	7.60%	-0.37	-0.18	47.6	-0.22	58.9	11.30%	0.03	-0.27	-851.2	-0.15	-460.9	29.68	26.54	WHEEZING EPISODE	Wheezing episode
38	7.43	4.86	1	1.42	142.1	1.06	106.8	35.30%	0.82	0.56	69	0.49	59.2	9.80%	-0.32	-0.41	126.5	-0.38	117.6	8.90%	0.04	-0.25	-574.9	-0.15	-352	26.51	24.38	WHEEZING EPISODE	Wheezing episode
39	4.17	2.92	1.05	1.03	97.3	0.9	85.4	11.90%	0.87	0.57	65.2	0.48	54.9	10.30%	-0.34	-0.31	91.2	-0.27	77.9	13.30%	0.04	-0.13	-324.2	0.-.05	-114.4	25.37	21.79	WHEEZING EPISODE	pneumonia
41	12.99	2.16	0.96	1.9	197.7	1.02	105.8	91.90%	0.79	0.75	94.6	0.75	94.7		-0.31	-0.6	193.4	-0.17	154.6	38.80%	0.05	-0.45	-969.5	-0.05	-100.1	35.53	24.81	COUGH VARIANT ASTHMA/WHEEZING EPISODE	OTHERS
43	5.53	5.43	1.29	1.31	101.4	1.11	86.3	15.10%	1.07	0.85	79.8	0.62	58.1	21.70%	-0.41	-0.44	107.3	-0.41	100.6	7.30%	0.02	-0.2	-912.7	-0.19	-898.7	29.85	27.84	PNEUMONIA	pneumonia
44	7.71	3.8	0.95	1.55	162.8	1.05	110.2	52.60%	0.77	0.68	87.7	0.56	73	14.70%	-0.31	-0.52	168.3	-0.28	91.4	76.90%	0.05	-0.23	-498.1	-0.11	-248.2	25.88	24.27	WHEEZING EPOSODE	Wheezing episode
45	1.65	2.73	1.24	0.74	60.2	1.22	98.4	38.20%	1.02	0.54	53.1	0.88	86.7	33.60%	-0.39	-0.12	31.6	-0.36	90.6	60.00%	0.02	-0.05	-220.8	-0.02	-86.6	23.39	21	WHEEZING EPOSODE	pneumonia
47	4.67	3.85	0.92	1.19	129.5	0.93	101.8	27.70%	0.75	0.71	94.8	0.58	78.4	16.40%	-0.3	-0.28	95.7	-0.35	118.8	23.10%	0.05	-0.17	-352.5	-0.12	-247.9	27.36	26.23	WHEEZING EPISODE	Wheezing episode
48	5.34	3.43	1.09	1.36	124.8	1.04	95.4	29.40%	0.89	0.72	81.3	0.92	103.8	22.50%	-0.35	-0.36	104.7	-0.47	134.2	30.50%	0.04	-0.19	-529.3	-0.09	-257	27.43	24.79	URI WITH WHEEZING EPISODE	Wheezing episode
49	2.55	2.26	1.17	1.01	86.4	0.95	81.1	5.30%	0.97	0.66	67.6	0.63	65	7.60%	-0.38	-0.11	28.9	-0.12	31.2	2.30%	0.03	-0.08	-247.8	-0.06	-181.1	24.47	24.22	PNEUMONIA	pneumonia
50	4.53	2.86	1	1.11	110.5	0.78	77.8	32.80%	0.82	0.66	81.1	0.45	54.7	26.40%	-0.32	-0.28	86.2	-0.35	109.5	23.30%	0.04	-0.16	-382.2	-0.08	-182.9	25.39	24.91	Wheezing episode	Wheezing episode
51	5.78	3.98	0.97	1.03	106.7	0.9	93.4	13.30%	0.79	0.44	55.4	0.41	51.7	3.70%	-0.31	-0.6	191.5	-0.4	129.3	62.20%	0.04	-0.15	-330.1	-0.13	-294.2	24.67	22.84	wheezing episode	pneumonia
52	9.12	4.58	1.07	1.77	165.4	1.24	115.4	50%	0.89	0.59	66	0.73	82.2	16.20%	-0.35	-0.23	65.1	-0.32	93.4	28.30%	0.04	-0.3	-748.1	-0.17	-429.1	25.88	25.05	pneumonia	Wheezing episode
53	4.09	3.36	1.08	0.86	79.4	0.81	75.2	4.20%	0.89	0.4	45	0.29	33.1	11.90%	-0.35	-0.42	121.6	-0.34	99.1	22.50%	0.04	-0.11	-283.4	-0.04	-114.9	23.92	21.1	wheezing episode	pneumonia
54	2.89	3.64	1.07	0.84	78.8	0.92	86.5	7.70%	0.87	0.41	47	0.42	48.4	1.40%	-0.34	-0.29	83.5	-0.42	123.1	39.60%	0.04	0	12.8	0.03	67.8	19.87	19.33	wheezing episode	pneumonia
55	3.06	3.19	1.29	1.03	80.3	0.96	74.2	6.10%	1.07	0.82	77.2	0.59	55.1	22.10%	-0.41	-0.43	103.8	-0.29	70	33.80%	0.02	-0.09	-398.1	-0.1	-482.5	24.88	24.01	wheezing episode	pneumonia
57	3.94	2.98	0.92	0.78	84.6	0.75	81.2	3.40%	0.75	0.32	42.8	0.46	62	19.20%	-0.3	-0.38	127.6	-0.36	120.6	7.60%	0.05	-0.1	-198.8	-0.08	-169.8	22.43	24.19	wheezing episode	Wheezing episode
58	4.71	5.97	1.17	1.35	115.4	1.38	118.2	3.20%	0.97	0.49	50.9	0.47	48.1	2.80%	-0.38	-0.45	118.8	-0.46	121.6	3.20%	*0.03*	*0.13*	*416.7*	*-0.03*	*-108.7*	*17.68*	*20.86*	wheezing episode	pneumonia
59	6.85	5.47	1.07	1.24	115.7	1.18	110.5	5.20%	0.87	0.53	60.8	0.55	63.2	2.40%	-0.34	-0.58	169.4	-0.45	132.4	37%	0.04	-0.2	-540.3	-0.17	-460	24.52	24.48	wheezing episode	Wheezing episode
60	3.26	2.58	1.12	0.87	77.8	0.83	74	3.80%	0.91	0.54	59.9	0.54	59	0.90%	-0.35	-0.41	115.3	-0.33	93.1	22.20%	0.03	-0.08	-237.7	-0.05	-147.9	22.88	22.07	pneumonia	pneumonia
61	5.07	2.51	1.31	0.99	75.8	0.59	1.07	0.40%	1.07	0.4	37	0.24	22.4	14.60%	-0.41	-0.49	119.8	-0.3	72.4	47.40%	0.02	-0.1	-604.3	0	-9.4	23.04	20.05	wheezing episode	Wheezing episode
62	3.88	2.13	1.06	1	94.2	0.64	60.3	34%	0.87	0.62	71.4	0.32	37.1	34.30%	-0.34	-0.42	124	-0.31	91.6	32.60%	0.04	-0.1	-271	0.08	221.5	23.35	17.82	wheezing episode	Wheezing episode
64	1.79	3	1.47	1.08	73.3	1.04	71.1	2.20%	1.22	0.97	80	0.85	70.3	10.30%	-0.46	-0.24	50.8	-0.44	94.2	43.40%	0.04	0.08	753.8	-0.07	-1063	28.16	24.92	wheezing episode	Wheezing episode
66	44.45	43.84	1.23	2.29	185.3	2.64	214.3	29.00%	1.02	1.03	101.4	1.1	107.8	6.40%	-0.39	-6.36	1614.2	-5.87	1491.4	122.80%	0.02	-1.12	-4525	-1.09	-4381	40.35	40.39	wheezing episode	Wheezing episode
67	0.08	5.93	1.15	0.66	57	1.38	119.9	62.90%	0.95	0.63	66.3	0.62	64.9	1.40%	-0.37	0	0.4	-0.33	89	88.60%	0.03	0.01	18.3	-0.21	-672.9	17.3	24.85	wheezing episode	Wheezing episode
69	1.56	1.69	1	0.7	70.4	0.74	73.8	3.40%	0.82	0.49	59.9	0.47	56.8	3.10%	-0.32	-0.21	66.5	-0.18	55.4	11.10%	0.04	0.01	27.9	0.03	58	19.38	19.07	wheezing episode	pneumonia
71	2.25	2.36	0.89	0.91	102.3	0.83	93.7	8.60%	0.72	0.66	91.6	0.59	82.3	9.30%	-0.29	-0.2	68.2	-0.3	103.4	35.20%	0.05	-0.07	-135.7	-0.05	-104.9	25.54	24.1	wheezing episode	pneumonia
72	5.51	3.42	0.98	1.02	103.9	0.87	88.6	15.30%	0.79	0.6	76.5	0.44	55.7	20.80%	-0.31	-0.6	192.1	-0.43	137.2	54.90%	0.04	-0.17	-406.6	-0.03	-65	25.97	20.7	wheezing episode	Wheezing episode
73	3.4	1.77	0.97	1	103.2	0.71	73	30.20%	0.79	0.65	82	0.48	60.4	21.64%	-0.31	-0.34	107.6	-0.26	82.6	25%	0.04	-0.1	-232.7	-0.01	-32	23.94	20.67	wheezing episode	Wheezing episode
74	0.48	2.25	1.05	0.48	45.9	0.72	68.7	22.80%	0.87	0.36	41.7	0.43	49.6	7.90%	-0.34	-0.02	5.2	-0.12	34.4	29.20%	0.04	-0.02	-60.7	-0.09	-233.8	21.16	23.04	wheezing episode	Wheezing episode
77	5.14	2.86	1.11	1.24	112.3	0.78	71	41.30%	0.91	0.49	53.5	0.34	37	16.50%	-0.35	-0.46	128.4	-0.27	76.4	52%	0.03	-0.02	-65.9	0	-13.2	20.43	20.12	wheezing episode	Wheezing episode
78	4.97	3	0.47	1.07	229.6	0.92	198.2	31.40%	0.41	0.65	160.4	0.63	155	5.40%	-0.18	-0.51	274.8	-0.36	197.7	77.1	-0.08	-0.16	196.4	-0.08	101.2	25.92	23.33	wheezing episode	Wheezing episode
79	8.4	7.37	1.29	1.73	134.3	1.54	119.9	14.40%	1.07	0.54	50.8	0.56	52.6	1.80%	-0.41	-0.12	28.9	-0.4	97.8	68.90%	0.02	-0.27	-1249	-0.22	-1008	24.9	24.18	wheezing episode	pneumonia
81	3.77	3.24	0.89	0.74	83.8	0.76	86.1	3.70%	0.72	0.28	38.7	0.34	47.6	8.90%	-0.29	-0.41	143.3	-0.32	111.9	31.40%	*0.05*	*-0.04*	*-71.6*	*-0.05*	*-101.3*	*20.95*	*21.84*	wheezing episode	pneumonia
82	3.29	3.02	0.47	0.69	146.6	0.72	153.7	7.10%	0.41	0.32	78.9	0.43	105.2	26.30%	-0.19	-0.37	194.3	-0.38	200.7	6.40%	-0.09	-0.08	96	-0.08	99.5	22.32	23.49	wheezing episode	pneumonia
83	2.37	0.65	0.35	0.74	214.2	0.58	166.9	47.30%	0.31	0.46	150.8	0.51	165.5	14.70%	-0.07	-0.04	64.8	0.02	-24.4	40.40%	0	-0.13	4895.1	-0.04	1368.9	24.39	28.03	wheezing episode	Wheezing episode
84	3.13	0.21	0.35	1.13	325.9	0.54	157	168.90%	0.31	0.88	288.7	0.49	159.3	129.40%	-0.07	-0.15	226	-0.02	28	198%	0	-0.15	9680.1	0	-83.1	29.01	19.76	wheezing episode	Wheezing episode
85	2.58	2.13	0.89	0.99	112.1	0.82	92.4	19.70%	0.71	0.56	79.4	0.51	72.3	7.10%	-0.28	-0.08	28.9	-0.24	83.8	54.90%	0.05	-0.07	-134.3	-0.04	-80.9	22.97	21.85	wheezing episode	Wheezing episode
86	3.92	2.95	1.01	1.08	107.4	0.84	83.7	23.70%	0.82	0.43	52.5	0.39	47.9	4.60%	-0.32	-0.03	10.4	-0.12	38.2	27.80%	0.04	-0.11	-272.5	-0.08	-181.9	24	22.56	wheezing episode	Wheezing episode
87	5.44	5.45	1.32	1.11	84	1.15	86.9	2.90%	1.1	0.42	38.6	0.41	37.5	1.10%	-0.42	-0.46	109.9	-0.47	112.1	2.20%	0.02	-0.1	-504.4	-0.07	-365	21.92	21.4	pneumonia	pneumonia
89	33.6	10.2	1.1	3.24	294.2	2.62	237.5	56.70%	0.91	1.28	140.7	1.11	122.4	18.30%	-0.35	-3.07	864.7	-1.01	283.5	581.20%	0.04	-0.64	-1785	-0.33	-926.3	53.8	60.62	pneumonia	Wheezing episode
90	4.41	2.34	1.11	1	90.6	0.73	66.1	36.50%	0.91	0.45	49.9	0.38	41.3	8.60%	-0.35	-0.41	114.1	-0.25	70	44.10%	0.03	-0.08	-222.8	0.03	78.2	21.82	19.14	pnemonia	pneumonia
91	5.19	3.89	1.23	1	81.3	0.91	73.6	7.70%	1.02	0.48	47.6	0.45	44	3.60%	-0.39	-0.6	151.7	-0.5	127.6	24.10%	0.03	-0.11	-436.7	-0.02	-92.4	22.92	20.61	pneumonia	pneumonia
92	4.04	3.1	1	0.9	90	0.74	74	16%	0.82	0.44	53.4	0.4	48.5	4.90%	-0.32	-0.43	134.3	-0.4	122.4	11.90%	0.04	-0.08	-172.1	-0.04	-101.2	21.79	21.31	pneumonia	pneumonia
93	1.97	2.79	1.23	0.63	51.3	0.83	67.5	16.20%	1.02	0.37	36.5	0.39	38.7	2.20%	-0.39	-0.19	47	-0.34	86.5	39.50%	0.03	-0.04	-148.6	0.09	650.6	21.57	18.05	pneumonia	Wheezing episode
94	5.45	7.05	1.18	1.25	105.9	1.48	125.6	19.70%	0.97	0.46	47.5	0.5	51.6	4.10%	-0.38	-0.62	165.4	-0.79	210.6	45.20%	0.03	0.04	139	0	5.2	19.3	19.98	wheezing episode	pneumonia
96	5.23	5.39	1.23	1.09	88.4	1.02	83.1	5.30%	1.02	0.48	47.5	0.36	35.6	11.90%	-0.39	-0.44	111.7	-0.55	139.2	27.50%	*0.03*	*-0.12*	*-478*	*-0.09*	*-334.1*	*23.36*	*21.94*	wheezing episode	pneumonia
97	2.39	1.82	0.95	0.77	81.1	0.81	84.9	3.80%	0.77	0.46	59.7	0.6	77.5	17.80%	-0.31	-0.26	84.3	-0.22	70.8	14.50%	0.05	-0.01	-31.9	-0.03	-67.4	20.47	22.19	wheezing episode	pneumonia
98	8.56	4.97	0.89	1.65	185	1.19	133.4	51.60%	0.73	0.55	75.3	0.35	47.2	28.10%	-0.29	0.67	-228.1	0.04	461.5	233.40%	0.05	-0.31	-586.2	-0.09	-176.4	26.52	22.4	wheezing episode	Wheezing episode
101	3.48	3.07	1	0.82	82.40%	0.64	64.2	18.20%	0.82	0.37	45.7	0.36	43.6	2.10%	-0.32	-0.4	124.9	-0.39	120.2	4.70%	0.04	-0.08	-195.7	-0.05	-123.3	23.32	22.17	pneumonia	pneumonia