COMPARISON OF EFFICACY OF ORAL AMOXICILLIN AND INTRAVENOUS AMPICILLIN IN COMMUNITY ACQUIRED PNEUMONIA WITH CHEST INDRAWING IN CHILDREN AGED 3-59 MONTHS

M.D., DEGREE EXAMINATION
BRANCH VII PAEDIATRIC MEDICINE

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY
CHENNAI

INSTITUTE OF CHILD HEALTH AND
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MADRAS MEDICAL COLLEGE
CHENNAI
MAY 2018

CERTIFICATE

This is to certify that the dissertation titled **"COMPARISON OF EFFICACY OF ORAL AMOXICILLIN AND INTRAVENOUS AMPICILLIN IN COMMUNITY ACQUIRED PNEUMONIA WITH CHEST INDRAWING IN CHILDREN AGED 3-59 MONTHS"** submitted by **DR.M. GOKILA VANI** to the Faculty of Pediatrics, **THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the requirements for the award of **M.D., DEGREE (PEDIATRICS)** is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I **DR.M. GOKILAVANI** solemnly declare that the dissertation titled **"COMPARISON OF EFFICACY OF ORAL AMOXICILLIN AND INTRAVENOUS AMPICILLIN IN COMMUNITY ACQUIRED PNEUMONIA WITH CHEST INDRAWING IN CHILDREN AGED 3-59 MONTHS"** has been prepared by me.

This is submitted to the Tamil Nadu **DR.M.G.R Medical University,** in partial fulfillment of the rules and regulations for the M.D Degree examination in Pediatrics.

Place: Chennai **DR. M. GOKILAVANI**

Date:

SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **PROF. DR.S. NARAYANA BABU M.D., DCH,**Dean, Madras Medical College, for allowing me to do this dissertation, utilizing the institutional facilities.

ACKNOWLEDGEMENT

It is with immense pleasure and privilege, I express my heartfelt gratitude, admiration and sincere thanks to **PROF. DR.T. RAVICHANDRAN, M.D., DCH.,**

Professor and Head of the Department of Pediatrics, for his guidance and support during this study.

I am greatly indebted to my guide and teacher, **PROF. DR.C. SUBBULAKSHMI, M.D, DCH.,** and my co-guide **PROF. DR.S. ELILARASI** Professor of Pediatrics for her supervision, guidance and encouragement while undertaking this study.

I would like to thank to my Assistant Professors **DR. SRIDEVI A NAARAYAN, MD, DR.D.PRABHAKAR, M.D, DR.D.PRIYADARSHINI, M.D, DR.N SHAJATHI BEGUM M.D** for their valuable suggestions and support.

I also thank all the members of the Dissertation Committee for their valuable suggestions.

I gratefully acknowledge the help and guidance received from **DR.S. SRINIVASAN, DCH.,** Registrar at every stage of this study.

I also express my gratitude to all my fellow postgraduates for their kind cooperation in carrying out this study and for their critical analysis.

I thank the Dean and the members of Ethical Committee, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai for permitting me to perform this study.

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CERTIFICATE OF APPROVAL

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Dear Dr.M.Gokilavani,

The Institutional Ethics Committee has considered your request and approved your study titled **"ORAL AMOXYCILLIN VERSUS INTRAVENOUS AMPICILLIN FOR CHEST INDRAWING PNEUMONIA IN CHILDREN AGED 3-59 MONTHS " NO. 09112016.**

The following members of Ethics Committee were present in the meeting hold on **01.11.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
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12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

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INTRODUCTION

Pneumonia is acute inflammation of the lung parenchyma usually caused by infections. There is no universally accepted definition of pneumonia worldwide. Indian classifications define it based on history of respiratory symptoms and clinical findings. WHO has defined pneumonia solely based on clinical findings based on respiratory rate and presence of chest retractions. (1)

The incidence of pneumonia in children below 5 years is estimated to be 0.29 episodes/child-year in developing countries. There are about 156 million new episodes each year worldwide. Among the developing world, India shares the highest burden with 43 million new episodes of pneumonia every year followed by China, Pakistan, Bangladesh and Indonesia (2). Among all community cases, 7-13% are severe enough to be life threatening and require hospitalization killing more than 2 million children every year. Pneumonia is a substantial cause of morbidity and mortality among children less than 5 years of age.

Recent estimates from the World Health Organization suggest that pneumonia is responsible for 19% of deaths in the above age group, leading to nearly 3 million deaths per year. Of these deaths, two thirds occur during infancy and more than 90% occur in the developing countries. In India, recent estimates in under-fives suggest that 13% of deaths and 24% of National Burden of Disease is due to pneumonia (3). Hospital based studies have

reported that 20–30% of admissions in under-fives are due to pneumonia. Case fatality rates in hospitalized children are reported to be between 8.7–47% (4).

Various interventions have been done by the World Health Organization (WHO) to reduce pneumonia related morbidity and mortality. Acute Respiratory Infection (ARI) control program was initiated in 1983, which includes identification of children with pneumonia by clinical features (rapid respiration and difficulty in breathing) and administration of antimicrobials with a presumption that majority of pneumonia in developing countries is because of bacterial pathogens, which led to a decline in the infant mortality rate by 10.7 (4.8–16.7) deaths per 1000 live births and decline in the mortality of under-fives by 36 deaths per 1000 live births.(5)

ETIOLOGY

Pneumonia can be caused by infectious and non- infectious agents. Most cases of pneumonia are caused by microorganisms like bacteria, viruses, fungi etc. The non-infectious causes include aspiration, foreign bodies, hydrocarbons, hypersensitivity reactions and drug/ radiation induced (4,5).

The common causes of pneumonia according to age are shown in table 1 below:

AGE GROUP	COMMON CAUSES OF PNEUMONIA	LESS COMMON CAUSE OF PNEUMONIA
<2 months	Klebsiella,Ecoli, staphylococci,gram negative bacteria	Pneumococci H influenza Anaerobic organisms
2 months to 5 years	Bacteria: Pneumococci,H. influenza, staph aureus, Klebsiella Viruses: Respiratory syncytial virus, Parainfluenza virus, Influenza virus	M.Tuberculosis, N.Menigitidis, Measles, Varicella zoster
>5 years	Pneumococci, Mycoplasma, Chlamydia	H influenza, S.aureus, M.Tuberculosis, adenovirus, EBV

Table 1: causative organisms of pneumonia

In children with HIV, bacteria remain the most common causative organism in pneumonia, but additional pathogens like Pneumocystis jiroveci should be considered particularly in children with low CD4 counts. Other causes in children include mycobacterium, fungal infections and viral infections. (6)

Pertussis should be considered in all infants with community acquired pneumonia especially if immunization is not complete. Mycobacterium tuberculosis can cause pneumonia in children if they are exposed to adults with the disease (7).

Risk factors related to the host and the environment that affect incidence of childhood clinical pneumonia in the community in developing countries (4)

Definite risk factors

Malnutrition (weight-for-age z-score < –2)

Low birth weight (≤ 2500 g)

Non-exclusive breastfeeding (during the first 4 months of life)

Lack of measles immunization (within the first 12 months of life)

Indoor air pollution

Crowding

Likely risk factors

Parental smoking

Zinc deficiency

Mother’s experience as a caregiver

Concomitant diseases (e.g. diarrhea, heart disease, asthma)

Possible risk factors

Mother’s education

Day-care attendance

Rainfall (humidity)

High altitude (cold air)

Vitamin A deficiency

Birth order

Outdoor air pollution

PATHOGENESIS:

Pneumonia results from inflammation of the alveolar space and may compromise air exchange. While often complicating other lower respiratory infections such as bronchiolitis or laryngotracheobronchitis, pneumonia may also occur via hematogenous spread or aspiration. Most commonly, this inflammation is the result of invasion by bacteria, viruses, or fungi, but it can occur as a result of chemical injury or may follow direct lung injury (e.g., near drowning). (8)

Four stages of lobar pneumonia have been described. In the first stage, occurring within 24 hours of infection, the lung is characterized microscopically by vascular congestion and alveolar edema. Many bacteria and few neutrophils are present. The stage of red hepatization (2-3 days), so called because of its similarity to the consistency of liver, is characterized by the presence of many erythrocytes, neutrophils, desquamated epithelial cells, and fibrin within the alveoli. (9,10)

In the stage of grey hepatization (2-3 days), the lung is gray-brown to yellow because of fibrino-purulent exudate, disintegration of red cells, and hemosiderin. The final stage of resolution is characterized by resorption and restoration of the pulmonary architecture. Fibrinous inflammation may extend into the pleural space, causing a rub heard by auscultation, and it may lead to resolution or to organization and pleural adhesions. Bronchopneumonia, a patchy consolidation involving one or more lobes, usually involves the dependent lung zones, a pattern attributable to aspiration of oropharyngeal contents. The neutrophilic exudate is centered in bronchi and bronchioles, with centrifugal spread to the adjacent alveoli (9).

In interstitial pneumonia, patchy or diffuse inflammation involving the interstitium is characterized by infiltration of lymphocytes and macrophages. The alveoli do not contain significant exudates, but protein-rich hyaline membranes similar to those found in adult respiratory distress syndrome (ARDS) may line the alveolar spaces. Bacterial super infection of viral pneumonia can also produce a mixed pattern of interstitial and alveolar air

space inflammation. Miliary pneumonia is a term applied to multiple, discrete lesions resulting from the spread of the pathogen to the lungs via the bloodstream.

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including the muco-ciliary clearance, the properties of normal secretions such as secretory immunoglobulin A and clearing of the airway by coughing. Immunologic defense mechanisms of the lung that limit invasion by pathogenic organisms include macrophages present in alveoli and bronchioles, secretory IgA and other immunoglobulins. Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium resulting in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes them particularly susceptible to severe infection. Atelectasis, interstitial edema, and ventilation perfusion mismatch causing significant hypoxemia often accompany airway obstruction. It can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions and modifying the bacterial flora (11,12)

When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. Streptococcus pneumoniae produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung often resulting in the characteristic lobar involvement. S. aureus pneumonia manifests in confluent bronchopneumonia which is often unilateral and characterized by presence of

extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatocoeles, empyema or at times bronchopulmonary fistulas. (9)

Mycoplasma pneumoniae attaches to the respiratory epithelium, inhibits ciliary action and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree as it does in viral pneumonia. (5,11)

CLINICAL FEATURES:

Children with pneumonia may present with fever with/ without chills, cough, fast breathing and in severe cases with chest retractions, nasalflaring,lethargy, irritability, inability to feed. Very severe cases may present with respiratory failure. Among these, fever and fast breathing are most consistent features. The atypical manifestations include vomiting, diarrhea, abdominal pain, neck retractions in younger children.

Children with bacterial pneumonia have very highgrade fever, chills, productive cough and systemic manifestations in the form of sepsis. Rapid progression is characteristic of bacterial pneumonia; wheezing is not a feature of bacterial pneumonia. Children with viral pneumonia may have a prodrome of symptoms like cough and rhinitis later developing fast breathing and wheezing. Children with mycoplasma and chlamydia infection may have

gradual onset head ache,malaise, non -productive cough, low grade fever and rhonchi (13)

The physical examination findings depend on the severity, stage of pneumonia and associated complications. Early in the course of illness decreased breath sounds, with crackles and rhonchi may be present on the affected lung fields.

With increasing consolidation or development of pleural effusion, pyothorax and pyopneumothorax, there will be dull note on percussion. Other physical abnormalities include paralytic ileus, neck rigidity and abdominal distension.

Differences between bacterial and viral pneumonia is shown in table 2 below : (14)

FEATURES	**BACTERIAL PNEUMONIA**	**VIRAL PNEUMONIA**
ONSET	Abrupt	Gradual
EPIDEMIC	Not seen	Common
ASSOCIATED CONDITIONS	Sepsis	Associated with URI, coryza
FEVER	High grade	May be absent
TOXEMIA	Common	Absent
RESPIRATORY DISTRESS	Common	Absent
LUNG SIGNS	Crackles++	Wheeze++

CXR	Confluent infiltrates.	Diffuse in peripheral areas.
PLEURAL INVOLVEMENT	May be seen	Not common
PROGNOSIS	Complications can be seen like empyema, pneumatocoele.	Usually self-limiting. Resolves in a week. Hyperinflation can be seen

Table 2: Differences between bacterial and viral pneumonia

DIAGNOSIS:

Pneumonia is usually a clinical diagnosis. The utility of various clinical features in making the diagnosis of pneumonia has been studied. Tachypnea is the most consistent useful sign of pneumonia with sensitivity of 64-81%. It has the advantage of high reproducibility, very less interpersonal variability and does not needhigh expertise and hence can be used at the community level by health workers in making the diagnosis of pneumonia. (15)

Chest indrawing has the sensitivity of 17-35% and specificity of 82-84% in identifying pneumonia. Auscultatory signs have lower sensitivity and specificity and poor reproducibility. Crackles are 43-57% sensitive and 75-80% specific in identifying pneumonia in the community. These criteria may not be useful in malnourished children. (9,16)

Fall in saturation or cyanosis is generally a late sign and may not help in diagnosing pneumonia and when present, it indicates severe pneumonia. Normal oxygen saturation does not correlate with milder disease.

In developing countries like India, the diagnosis of pneumonia is based on the WHO's age specific criteria for tachypnea which can also be used at community level for diagnosis and referral.

Diagnosis of tachypnea in the various pediatric age groups

Age - respiration rate (breaths/min)

0-2months ≥ 60

2-12months ≥ 50

1-5years ≥ 40

Chest X-ray is done to confirm the diagnosis. The CXR in viral pneumonia is characterized by hyperinflation, bronchial wall thickening and focal areas of atelectasis. Confluent lobar consolidation is consistent with pneumococcal pneumonia. Chest X-ray does not differentiate causative agents of pneumonia.Since CXR does not change the course of pneumonia,it is not recommended for the diagnosis of pneumonia.It should be reserved for children with ambiguous findings, persistent pneumonia, pneumonia that is unresponsive to antibiotics and those with suspected complications like pleural effusion. (17)

For rational treatment of pneumonia, causative organism must be identified by clinical features or rapid and less expensive laboratory tests. It is not easy to distinguish bacterial and viral pneumonias based on clinical features and CXR findings. Bacterial pneumonia in children is associated with moderate to high grade fever, polymorph nuclear response in blood, increased level of acute phase reactants like pro-calcitonin and C-reactive proteins in blood and alveolar consolidation on radiographs on chest. Viral pneumonia is associated with young age, breathlessness and wheezing. However, all the clinical features and laboratory tests do not have desirable sensitivity and specificity to use them in clinical practice. (11)

The common methods used for the identification of the etiological agents include blood culture, lung puncture, nasopharyngeal aspirates, immunoassays of blood and urine. All these methods have their own drawbacks. The blood culture is not a reliable investigation because of its lower yield (ranging from 5% to 30% in various studies) in bacterial pneumonias. (15) Lung puncture is an invasive procedure associated with high incidence of pneumothorax and pulmonary hemorrhage and hence cannot be performed routinely in all cases. Nasopharyngeal aspirates can be used for the isolation of viruses, chlamydia, and mycoplasma, but a possibility of concomitant bacterial pneumonia cannot be ruled out with confidence. There are various immunoassays for identifying bacteria, viruses, mycoplasma, chlamydia and P. jiroveci but are expensive and need standardization in community studies. (15)

In view of difficulties faced with identification of organisms, the high cost and lack of availability of the investigations, the laboratory tests are not ordered routinely for the diagnosis of CAP. Most of the cases are diagnosed on clinical grounds and treated accordingly. In children with poor response, underlying systemic disease and immunocompromised hosts, an aggressive attempt should be made to identify etiological agents.

CLASSIFICATION OF PNEUMONIA:

In developing world, in view of very high incidence of pneumonia it is recommended to make the diagnosis of pneumonia at community level based on clinical features alone (14).According to IMCI (Integrated management of childhood illness), pneumonia is classified as

No pneumonia:

No fast breathing and no indication of severe and very severe pneumonia.

Pneumonia:

Fast breathing and no indication of severe and very severe pneumonia

Severe pneumonia:

lower chest indrawing or nasal flaring and no sign of very severe pneumonia.

Very severe pneumonia:

Central cyanosis, or not able to breastfeed or drink or convulsions, or lethargy or unconsciousness or severe respiratory distress (2).

Figure 1 shows the IMNCI classification of pneumonia:

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print)
• Any general danger sign or • Chest indrawing or • Stridor in calm child	SEVERE PNEUMONIA OR VERY SEVERE DISEASE	▸ **Give first dose of Cotrimoxazole** ▸ **Refer URGENTLY to hospital**
• Fast breathing	PNEUMONIA	▸ **Give Cotrimoxazole for 5 days.** ▸ Soothe the throat and relieve the cough with a safe remedy. ▸ Advise mother when to return immediately. ▸ Follow-up in 2 days.
• No signs of pneumonia or very severe disease.	NO PNEUMONIA: COUGH OR COLD	▸ If coughing more than 21 days, refer for assessment. ▸ Soothe the throat and relieve the cough with a safe remedy ▸ Advise mother when to return immediately. ▸ Follow-up in 5 days if not improving.

Figure 1: Classification of pneumonia (IMNCI classification)

Recently in 2015, WHOpublished the revised the classification and treatment of childhood pneumonia at health facilities. The new classification is therefore simplified to include only two categories of pneumonia, “pneumonia” with fast breathing and/or chest indrawing which requires home therapy with oral amoxicillin and “severe pneumonia”, pneumonia with any general danger sign, which requires referral and injectable drug therapy.(23)

Figure 2 shows the recent WHO classification of pneumonia:

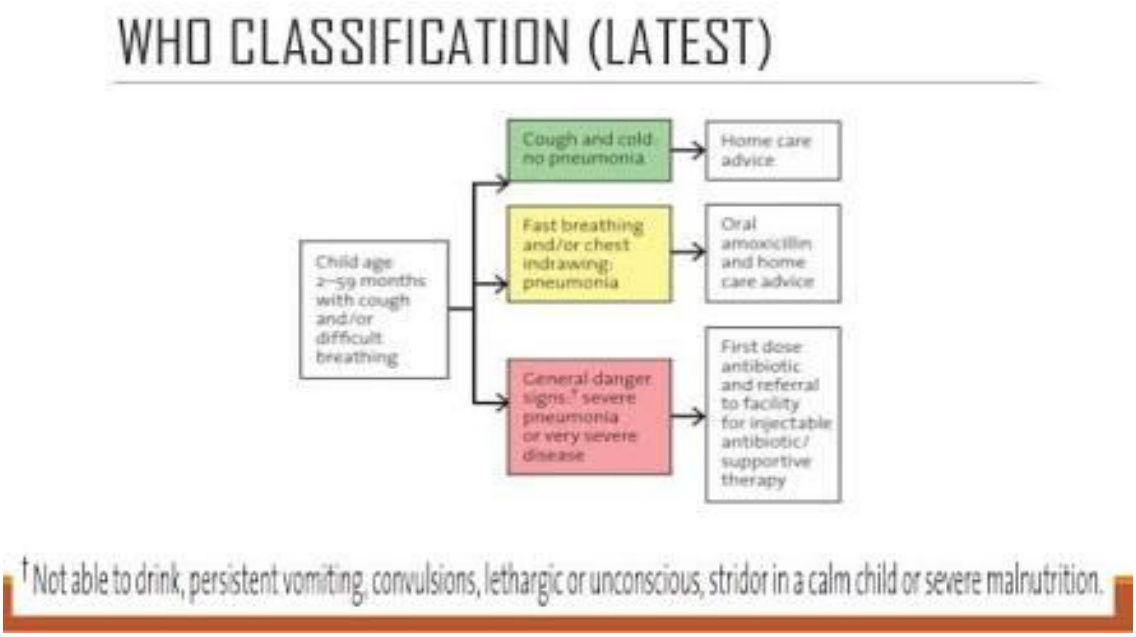

Figure 2: Recent WHO classification of pneumonia

The following figure shows the difference between the previous and recent WHO classification of pneumonia:

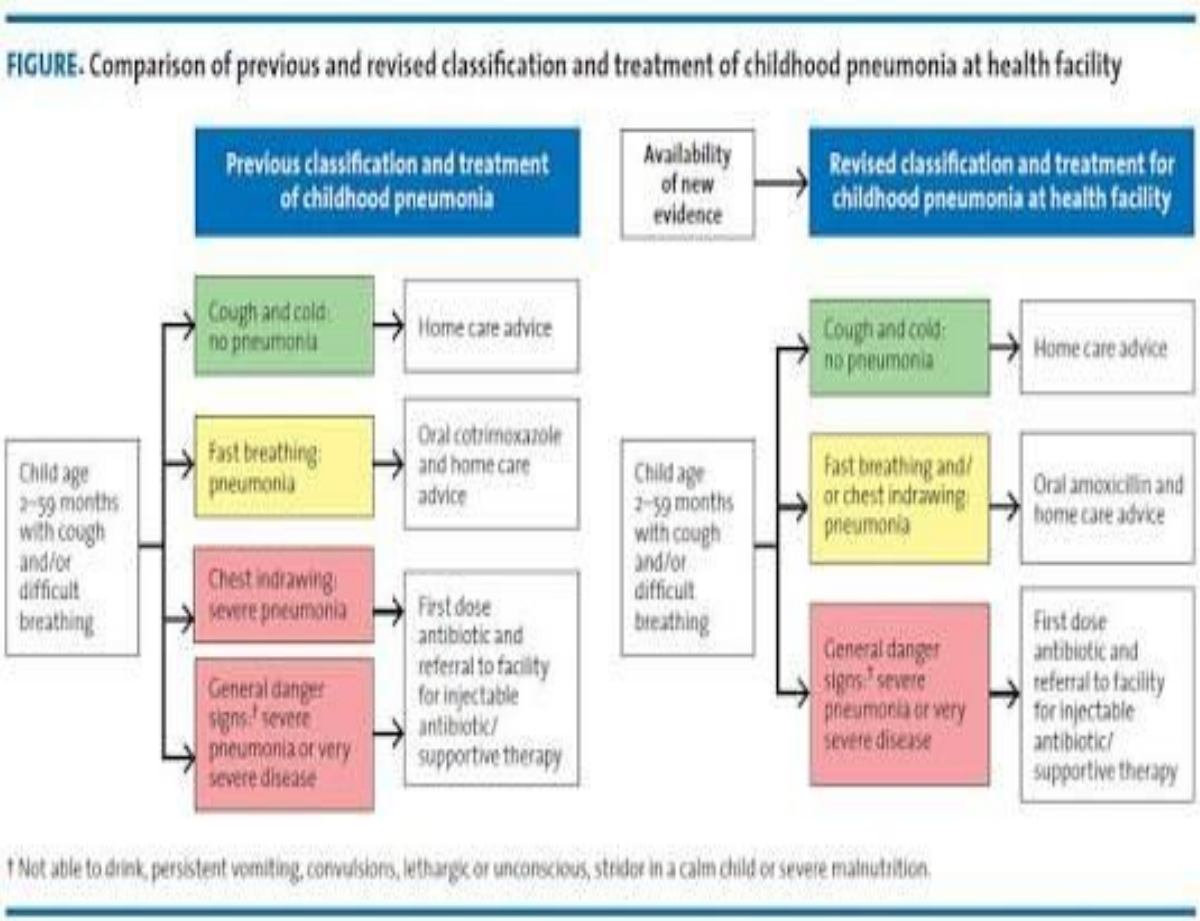

Figure 3: Difference between previous and latest WHO classification

Table 3 showing classification of pneumonia according to WHO and IMNCI:

WHO	IMNCI
Pneumonia – fast breathing and chest indrawing pneumonia.	No pneumonia: no fast breathing and no indication of severe and very severe pneumonia.
Severe pneumonia- pneumonia with danger signs- • Central cyanosis • Not able to breastfeed or drink convulsions • Lethargy • Unconsciousness • Severe respiratory distress.	Pneumonia: fast breathing and no indication of severe and very severe pneumonia.
	Severe pneumonia : lower chest indrawing or nasal flaring and no sign of very severe pneumonia.
	Very severe pneumonia: • Central cyanosis • Not able to breastfeed or drink convulsions • Lethargy • Unconsciousness • Severe respiratory distress

Table 3: WHO and IMNCI classification of pneumonia

MANAGEMENT:

In developing world, in view of very high incidence of pneumonia it is recommended to make the diagnosis of pneumonia at community level based on clinical features alone. The diagnostic criteria suggested by WHO are very cost effective for CAP. There is no indication for any test in a child with suspected community acquired pneumonia. Children with non-severe pneumonia with no danger signs should be treated on outpatient basis with oral antibiotics and antipyretics.

SELECTION OF ANTIBIOTIC:

Administration of appropriate antibiotic in early period of pneumonia alters the outcome of the disease particularly when the causative organism is bacteria. Antibiotics may not have role in pneumonia caused by viruses. Unnecessary antibiotics administration in children may lead to selection of resistant organism and thus promotes drug resistance and serious illness in the future. However, in view of public health implications of better outcome of pneumonias by early administration of antibiotics and lack of reliable laboratory test in identification of causative agents, antibiotics are administered empirically in most instances. Treatment decisions are made based on child's age and epidemiological factors. Factors that helps in choosing appropriate antibiotics are

1.Knowledge of etiological agents

2.Sensitivity of pathogens to antibiotics.

3. Immune status

4. Nutritional status

5. Previous antibiotics used in recent past

6.History of hospitalization, duration of illness.

7. Associated illnesses

8. Cost and safety of antibiotics.

LIKELY ETIOLOGICAL AGENTS:

The common etiological agents of pneumonia in children below 2 months include gram negative bacilli. In children between 2 months- 5 years, it is commonly caused by S. pneumoniae, Staphylococcus aureus and atypical organisms. In children above 5 years, the common agents are S.pneumoniae, Staphylococcus aureus and mycoplasma.(8)

SENSITIVITY OF PATHOGENS:

Common etiological agents including S. pneumoniae and H. influenza are sensitive to wide range of antibiotics including semi synthetic penicillin (amoxicillin, ampicillin), cephalosporins (cephalexin,cefaclor, cefuroxime), macrolides (erythromycin, azithromycin, roxithromycin), cotrimoxazole and chloramphenicol. Gram negative bacilli are sensitive to ampicillin, aminoglycosides and cephalosporins.

Atypical organisms such as chlamydia and mycoplasma are sensitive to macrolides and tetracycline. The latter is not used in children below 8 years of age. Thus, macrolides are the drug of choice for the treatment of atypical organisms. Newer quinolones such as gatifloxacin and levofloxacin have an advantage of good coverage for S. pneumoniae. However, their use in children is limited and need more trials.(9)

SEVERITY OF ILLNESS:

In most circumstances, microbial etiology of pneumonia remains similar despite varying degree of severity of illness. However, it is logical to select most appropriate antibiotics that have lesser chance of failure due to possible resistant organisms in more severe disease.

UNDERLYING DISEASE:

Knowledge about the underlying disease is essential in selecting antibiotic as many chronic diseases have special predilection to particular organisms. Children with hemoglobinopathies or nephrotic syndrome are more susceptible to pneumococcal organisms.A child with cystic fibrosis is more likely to have infection with staphylococcus,H. influenza or pseudomonas. A child with HIV infection may be due to gram negative bacilli, P. jiroveci or fungi in addition to usual pathogens. The progression of disease is rapid in this group due to immunodeficiency and hence most efficient antibiotic combinations are used as first line treatment (10). Children with neutropenia should be treated with antibiotics that are effective against gram- negative

bacilli, staphylococcus along with common pathogens like S. pneumoniae, and H. influenza. Hence the drug of choice may be ceftazidime with aminoglycosides with/ without cloxacillin or vancomycin.(16,17) If patient does not respond over 2-3 days, the next may be to consider antifungal antibiotics and treatment of P. jiroveci pneumonia.

NUTRITIONAL STATUS:

Malnourished children are predisposed to more frequent and severe episodes of pneumonia. The etiology of pneumonia in malnourished children is generally similar to that in well nourished, with an added predisposition for gram negative organisms. Pneumonia in malnourished children may progress to severe disease rapidly. The symptoms of pneumonia may be masked in severely malnourished children possibly due to a blunted inflammatory response (18).

PREVIOUS ANTIBIOTICS:

History of antibiotics for the current episode or in the recent past (previous 2-4 weeks) may give an idea about possible resistant organisms. If a patient had received repeated course of antibiotics patient's microbial flora may be resistant to those antibiotics. If a patient has already received cotrimoxazole or amoxicillin, it is better to give amoxicillin –clavulanate, cefuroxime or cefpodoxime rather than giving some antibiotics. (18)

HISTORY OF HOSPITALIZATION:

After hospitalization the microbial flora of the patient changes to gram negative bacilli. Hence, pneumonia in hospitalized child or hospitalized in recent past is more likely to be due to gram negative bacilli. The staphylococcal infection in hospital setting is likely to be resistant to penicillin and needs vancomycin or linezolid. In such situations, cefuroxime or amoxicillin-clavulanic acid may be used as primary drugs in non -severe illness and combination of quinolone or third-generation cephalosporin with vancomycin may be used in severe pneumonia.

DURATION OF ILLNESS:

A short duration of illness suggests a possible bacterial etiology. Prolonged illness of more than 2 weeks may be due to infection with M. tuberculosis, atypical organism or certain viral infections like adenovirus.

INDICATIONS FOR INTRAVENOUS ANTIBIOTIC THERAPY:

Intravenous antibiotic therapy is warranted if the child has severe pneumonia, disturbed consciousness, improper swallowing, frequent vomiting and suspected drug malabsorption. Switch to oral when the child starts accepting orally and shows significant clinical improvement. Complete intravenous therapy is needed if the patient is newborn.

The revised guidelines proposed by WHO in 2015 (23) for the management of community acquired pneumonia are

1) Children with fast breathing pneumonia with no chest in drawing or general danger signs should be treated with oral amoxicillin at least 40 mg/kg/dose twice daily (80 mg/kg/day) for five days. In areas with low HIV prevalence give amoxicillin for 3 days.

   Children with fast breathing pneumonia who fail on first line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second line treatment.
2) Children aged 2-59 months with chest indrawing pneumonia should be treated with oral amoxicillin at least 40 mg/kg/dose twice daily(80 mg/kg/day) for five days.
3) Children aged 2-59 months with severe pneumonia should be treated with parenteral ampicillin and gentamicin as first line treatment. Ampicillin 50mg/kg or benzyl penicillin 50,000 units/kg IM/IV every six hours for at least 5 days and gentamicin 7.5mg/kg IM/IV once a day for at least 5 days. Ceftriaxone should be used as a second line treatment in children with severe pneumonia having failed on first line treatment.
4) Ampicillin (penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first line treatment for HIV infected and exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.For HIV infected and exposed infants and for children with chest indrawing pneumonia or

severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second line treatment.

5) Empiric cotrimoxazole treatment for suspected pneumocystis jiroveci pneumonia is recommended as an additional treatment for HIV infected and exposed children aged from 2 months-1 year with severe and very severe pneumonia. Empirical cotrimoxazole treatment for pneumocystis jiroveci is not recommended for HIV infected and exposed children over 1 year of age with chest indrawing or severe pneumonia.

MANAGEMENT OF PNEUMONIA ACCORDING TO INDIACLEN TASK FORCE ON PNEUMONIA: (2)

Pneumonia:

Cotrimoxazole5-7 mg/kg/day for 5 days or amoxicillin 30-40 mg/kg/day in 2-3 divided doses for 3 days.

Severe pneumonia:

Admission- iv ampicillin 50 mg/kg every 6 hours, Inj.Gentamicin to be added after 48 hrs. if no improvement.

Very severe pneumonia:

Iv ampicillin 50 mg/kg every 6 hourly and inj. Gentamicin 7.5 mg/kg/day once a day is started together.

The table 4 compares the treatment of pneumonia according to WHO and INDIACLEN task force of pneumonia: (2,23)

WHO	**INDIACLEN TASK FOCE ON PNEUMONIA**
Pneumonia-oral amoxicillin 40 mg/kg/ dose twice daily for 5 days	Pneumonia- cotrimoxazole5-7 mg/kg/day for 5 days or amoxicillin 30-40 mg/kg/day in 2-3 divided doses for 3 days
Severe pneumonia-parenteral ampicillin 50mg/kg or benzyl penicillin 50,000 units per kg im/iv every 6 hours for atleast 5 days. Gentamicin 7.5 mg/kg im/iv once a day for 5 days.	Severe pneumonia-admission- iv ampicillin 50 mg/kg every 6 hours, inj . Gentamicin to be added after 48 hrs if no improvement.
	Very severe pneumonia-iv ampicillin 50 mg/kg every 6 hourly and inj. Gentamicin 7.5 mg/kg/day once a day is started together.

Table 4: Treatment of pneumonia according to WHO and INDIACLEN.

INDICATIONS OF ADMISSION IN HOSPITAL: (19)

Age less than 2 months

Toxic appearance

Hypoxemia

Oxygen saturation <92%

Cyanosis

Respiratory difficulty

Apnoea

Grunting

Nasal flaring

Dehydration,vomiting or poor feeding

Immunocompromised status

Failure to respond to oral antibiotics

Inadequate observation or supervision by family

INDICATION FOR ADMISSION IN INTENSIVE CARE UNIT:

Pao2/ fio2< 250

Mechanical ventilation

CXR showing bilateral, multilobar pneumonia with increase in size of the opacity> 50% in 48 hrs prior to admission.

Hypotension

Vasopressor requirement

Acute renal failure

MANAGEMENT OF PNEUMONIA IN CHILDREN MORE THAN 5 YEARS:

The cause of pneumonia in children above 5 years are similar to adults including pneumococci and mycoplasma. If a patient does not improve with antibiotics or there are clinical features suggesting of atypical organisms, a course of atypical antibiotics may be given to these patients.(18)

MONITORING OF RESPONSE:

Clinical improvement may take upto 48-96 hrs. Fever can last upto 2-4 days, leucocytosis usually normalises by day 4, abnormal physical findings may persist for more than 7 days. Most non severe CAP showclinical resolution of symptoms in 2-3 days. Radiographs may worsen even though clinical picture is improving and CXR usually returns to normal within 6 weeks in patients and hence there is no role of follow-up CXR to look for recovery.

CAUSES OF FAILURE TO IMPROVE:

The possible cause for failure to improve is inadequate therapy which may be due to inappropriate antibiotic selection, inappropriate dosing and poor compliance. It can also be due to development of complications like empyema or lung abscess. If there is impaired host mechanism or there is development of drug resistance in the community, there may be delayed response or poor response. Non-bacterial pneumoniahas longer course than expected. Bronchial obstruction due to endobronchial lesions, foreign body or mucus plug and pre-existing lung diseases like cystic fibrosis, ciliary dyskinesia or bronchiectasis may take longer than usual to improve.

SUPPORTIVE THERAPY:

Although antibiotics are the mainstay of the treatment, children should be given supportive therapy for the associated problems. Children with pneumonia may have fever, poor oral intake, vomiting, electrolyte disturbance, hypoxia and respiratory failure. It takes some time for the antibiotics to act.

Fever should be treated with paracetamol in the doses of 10-15 mg/kg/ dose. It can be repeated at 4-6 hours.

Cough is other commonest symptom associated with pneumonia. Cough suppressants should be avoided. Common household remedies like tulsi, ginger and honey can be given to the child. If there is bronchospasm, inhaled bronchodilators like salbutamol can be given (20).

Vomiting in pneumonia usually follows coughing and does not require any specific treatment. If there is persistent vomiting, antiemetic can be given once acidosis, electrolyte disturbances and CNS causes are ruled out.

Associated comorbid conditions like diarrhoea, malnutrition, congenital heart diseases, immunodeficiency increases the case fatality in children with pneumonia.

There may be hyponatremia due to inappropriate ADH secretion. A careful monitoring and fluid restriction is the intervention required in these children.

Hypoxia may be present in children with severe pneumonia. If untreated, it may be associated with increased case fatality rates. Oxygen should be administered to all children with severe tachypnea (RR>70/min), chest in drawing, poor feeding or cyanosis. Oxygen may be administered by nasal prongs, nasopharyngeal tubes (low flow i.e. 1-2 L/min), oxygen hood, or face mask (high flow 4-8 L/min).Small children tolerate oxygen with hood better than nasal / nasopharyngeal cannula/ face mask. However, it should be kept in mind that oxygen saturation gives idea about oxygenation and does not

give any idea about carbon di oxide; even with respiratory failure, the saturation may be normal with high flow oxygen inhalation. Therefore, it is advised that in critically ill children, a baseline monitoring of arterial blood gas should be done(13).

Feeding requires close attention particularly in developing countries. Even anorectic children accept breast milk. All feeding should be given at greater than usual frequencies. If they unable to suck at breast, expressed breast milk should be given with a cup and spoon. In children with pneumonia not requiring oxygen frequent small energy dense feeds should be given. Children sick enough to need oxygen usually do not tolerate oral and nasogastric feedings, thus requiring intravenous fluids. In a small proportion of children, pneumonia persist despite responsible antibiotic therapy. Unusual etiological agents such as Chlamydia, pneumocystis, mycobacterium tuberculosis or foreign bodies may be involved in those instances. The latter possibilities should be explored. (24)

PREVENTION OF PNEUMONIA:

Routine immunisation against pertussis, measles has decreased significant number of deaths due to community acquired pneumonia. The common pathogens like H. Influenza and pneumococci causing pneumonia are also vaccine preventable. In western countries with routine use of H. influenza type b vaccine, the pneumonia and related deaths due to H. influenza have dropped significantly. Vaccines against pneumococci are also effective in

preventing invasive diseases due to pneumococci. Therefore, these vaccines should be administered preferably to all children. (40)

DRUGS USED IN THIS STUDY:

Aminopenicillins:

Aminopenicillins share the same basic core structure as ampicillin (2-amino derivative of benzyl penicillin). They feature a positively charged amino group that makes it easy to enter bacterial porin channels but does not protect it against the action of bacterial beta-lactamases. They have broad-spectrum activity against both gram-positive and gram-negative bacteria and their potency is enhanced by beta-lactamase inhibitors like clavulanic acid. They are very useful in the management of respiratory infections. The aminopenicillins include ampicillin, cyclacillin, amoxicillin, pivampicillin, andbacampicillin. Bacampicillin and pivampicillin are pro-drugs of ampicillin. Ampicillin was the first amino penicillin produced (1961). It is active against both Gram-positive and Gram-negative bacteria including S. pneumoniae and H. influenzae in respiratory tract infections. It is also effective against bacteria causing urinary tract infections, meningitis, salmonellosis and endocarditis. Its spectrum of activity is enhanced by combination with sulbactam, a beta-lactamase inhibitor. It is available in oral and intravenous formulations. Oral bioavailability is 40%. About 15-20% of ampicillin is bound to plasma protein. About 12-50% of the drug undergoes hepatic metabolism. The biological half-

life is about 1hour. Seventy-five to 85% of drug is excreted unchanged in the urine. (21)

AMOXICILLIN:

Amoxicillin is a 6-aminopenicillanic acid (6-APA) and usually the drug of choice within the amino penicillin class for the treatment of respiratory infections because of its better absorption when taken orally (95% absorbed). Parenteral preparation is available for intramuscular and intravenous use. Less than one-third is metabolized in the liver and more than half is excreted unchanged in the urine. It has a half-life of 61.3 minutes. Amoxicillin is a moderately broad spectrum antibiotic against susceptible Gram-positive and Gram-negative bacteria including Streptococcus, Bacillus subtilis, Enterococcus, Haemophilus, Helicobacter and Moraxella. Citrobacter, Klebsiella, Pseudomonas aeruginosa, some E. coli and Staphylococcus aureus are resistant to it. Combination of Amoxicillin with a beta- lactamase inhibitor like clavulanic acid (Co-Amoxiclav) improves its spectrum of activity. Drug-drug interactions with anticoagulants (e.g. Warfarin), allopurinol, methotrexate, uricosuria drugs and typhoid vaccine have been observed with Amoxicillin. It comes in oral suspension (for young children) and capsule. It is also available as salt for parental administration. (21,22)

REVIEW OF LITERATURE

- M.Atkinson, M. Lakhanpal, A. Smyth conducted a multi-centric pragmatic randomized controlled equivalence trial to ascertain whether therapeutic equivalence exists for the treatment of community acquired pneumonia by oral and intravenous routes. This study was the first of the kind in comparing oral and intravenous antibiotics. This study was conducted in eight pediatric centers in England. 246 children who had fever, respiratory symptoms and radiologically confirmed pneumonia were included in the study. Those children with wheeze, oxygen saturation <85%, those in shock, immunodeficiency, chronic lung condition and age less than 6 months were excluded from the trial. The children were randomized to receive oral amoxicillin for 7 days or IV benzyl penicillin. The primary outcome of this study was the time foe temperature to be < 38^0c for 24 hours and cessation of oxygen requirement. Secondary outcomes were time in the hospital,complications, duration of oxygen requirement and time to resolution of illness.The result of the study showed equivalence between oral amoxicillin and intravenous penicillin. The median time for the temperature to come down was 1.3 days in both the groups (P value<0.001). Three children in the oral group were changed to IV antibiotics and seven children in the intravenous group were changed to different antibiotics. The time for complete resolution was around 9 days in both the groups. This trial concluded that oral and intravenous

penicillin are equivalent in the treatment of community acquired pneumonia and thus oral amoxicillin can be preferred as it is painless and non-invasive treatment and also reducing the direct and indirect costs of treating pneumonia in the population (33).

- AddoYobo et al conducted a multi-centric, randomized, open label equivalency study carried out at four geographically dispersed countries Bangladesh, Egypt, Ghana and Vietnam between 2005 and 2008to determine whether oral amoxicillin and parenteral penicillin were equivalent in the treatment of severe pneumonia in children aged 3-59 months.873 children were included in the study based on the case definition given by WHO. Evaluation was carried out at 1,2,3,6 and 14 days to look for cumulative treatment failure and relapse rates. The primary outcome of the study was the treatment failure at 48 hrs. A secondary endpoint was treatment failure between day 6 and day 14. This study found 19% failure rates in each group. The most common reason for treatment failure was the persistence of lower chest indrawing at day 6, being abnormally sleepy and central cyanosis. The overall failure rates ranged between 6.4% to 13.2% and this study demonstrated that home based treatment of severe pneumonia can be applied to a wide variety of settings. This study also demonstrated high rates of treatment compliance for twice daily dosing of amoxicillin. There were no deaths during this study and none had serious adverse effects following drug administration. (25)

- Hazir et al carried out a randomized, open label equivalency trial at seven sites at Pakistan comparing hospitalization with parenteral penicillin to home treatment with oral amoxicillin. 2037 Children of age 3-59 months with chest indrawing pneumonia were randomized to treatment in hospital with two days of injectable penicillin followed by three days of oral amoxicillin or were sent home with a five day twice daily course of oral amoxicillin. Follow-up were done at 1,3,6 and 14 days of enrolment. The primary outcome of this study was treatment failure by day6. The secondary outcome of the study was treatment failure between day 6 and day 14.There were 8.6% failure in hospitalized group and 7.5% in the ambulatory group. 5 children died during this study (4 in hospitalized group and 1 in ambulatory group). But none of the deaths were related to treatment allocation. There were no adverse reactions reported in this study.They also found several baseline characteristics predictive of treatment failure namely young infancy (3-5 months), being significantly underweight for age and very fast breathing. The reason for treatment failure was either due to development of danger signs or persistence of lower chest retractions. Also this study demonstrated that antibiotic usage 7 days prior to randomization was a significant factor affecting the primary outcome. (26)
- A study in England was conducted in 2007. It compared oral amoxicillin with intravenous penicillin in the management of severe pneumonia.

The randomized controlled, non-blinded equivalence trial was conducted in eight Pediatric centers. Children were randomly assigned to a 7day treatment of either oral amoxicillin or iv benzyl penicillin. The primary outcome was the time required for temperature to be below 38 c for 24 hours. The study found the two treatments to be equivalent, each having a median of 1.3 days to achieve the primary outcome. The study recommended that children can be treated with oral amoxicillin instead of IV benzyl penicillin as oral treatment was both painless and non-invasive. (27)

- Archana B Patel,Akash bang,Meenu Singh, Ashraf Malik et al (2015)compared the clinical and cost outcomes of a seven-day treatment with the first 48hrs of treatment given in the hospital(hospital group) or at home (home group). It was anOpen label, multi-centric, two arm randomised control trial at six tertiary hospitals in India. A total of 1118 children aged 3-59 months with chest indrawing pneumonia were randomized to home and hospital groups. Clinical outcomes, treatment adherence, and patient safety were monitored through home visits on day 3,5,8 and 14 with an additional visit to home group after 24 hours. The primary outcome of this study was treatment failures upto 7 days and secondary outcome was treatment failures between 8 and 14 days. The cost outcomes included direct medical, direct non-medical and indirect costs.Overall treatment failures were around 11.5%. The predictors of treatment failure were age of 3-11 months, receiving

antibiotics 48 hrs prior to randomization and use of high polluting fuels. This study concludes that cost of treatment of severe pneumonia with oral amoxicillin who were initially admitted for 48 hours and then home based for 5 days was significantly higher than children treated with oral amoxicillin for 7 days at home. (28)

- Campbell et al. conducted a quasi-randomized control trial with chest in drawing pneumonia in Gambia comparing oral cotrimoxazole against intravenous procaine penicillin.134 children of age group 1 months-4 years with acute respiratory illness less than 1 week with signs of respiratory distress (intercostal indrawing and nasal flaring) were taken for the study. Children were randomly allocated to 5daycourse of oral cotrimoxazole and single IM injection of procaine penicillin followed by 5 days of oral amoxicillin. There was no difference in symptoms, signs or laboratory findings and no difference in terms of final outcome after 2 weeks of follow up. (27)
- Agweyu et al. did an open – label, multicenter, randomized controlled non-inferiority trial at 6 Kenyan hospitals. Children of age 2-59 months with severe pneumonia were taken for the study. One group of children received oral amoxicillin (40-45mg/kg) or intramuscular benzyl penicillin at 50,000 IU/kg 4 times a day. Primary outcome is treatment failure measured at 48 hours. Treatment failure was 11.4% and 11.0% in oral and intravenous group respectively.4 children died during the study

of which 3 belonged to benzyl penicillin group. The presence of wheeze is associated with less treatment failure in this study. (29)

- P.K. Lorgelly et al. conducted a cost- minimization analysis alongside a randomized controlled non-blinded trial in eight pediatric centers in England.232 children diagnosed with pneumonia were admitted and randomized to receive oral amoxicillin or intravenous benzyl penicillin. This study considered the cost of health service, patients and society from pre-admission until the child was fully recovered. The drugs had equivalent efficacy. Children in hospital admission had significant longer duration of hospital stays and more expensive than oral treatment. (30)
- A meta-analysis of four randomized controlled trials was conducted to determine the efficacy of oral antibiotics in under-five children with pneumonia and chest indrawing.4 clinical trials (Addo-Yobo et al, Hazir et al, Campbell et al, and Agweyu et al) involving 4400 children who were diagnosed to have severe pneumonia but were feeding well and not hypoxic were included for the study. In two studies oral antibiotics were administered on ambulatory basis while in two, oral antibiotics were used in hospitalized children. The primary outcome measure was treatment failure (persistence of symptoms, development of danger signs hypoxia and withdrawal from the study). Secondary outcome were relapses, death, need for hospitalization and severe side effects. All the 4 RCTs included children under 5 years of age. The proportion of infants

were similar in both groups (OR 1.03; CIO.86,1.22). The other baseline characteristics like sex distribution, nutritional status, presence of wheeze were similar in both groups. Three studies compared oral amoxicillin with parenteral penicillin/ ampicillin. Only one study compared cotrimoxazole with procaine penicillin. Failure rate in oral antibiotic group was 13% and in parenteral antibiotic group was 13.8%. Relapse rates, hospitalization or serious adverse effects were same in both groups. The results of this analysis was not influenced by treatment in hospital or treatment in society, type of antibiotics, etiological agents and presence of wheeze. This analysis concluded that children with chest indrawing pneumonia from low and middle income countries with low HIV prevalence may be managed with oral antibiotics at home with monitoring by health care workers (31).

STUDY JUSTIFICATION

Various studies done worldwide have proven that oral amoxicillin can be safely used instead of parenteral penicillin in children with chest indrawing pneumonia of age 3-59 months based on which WHO revised guidelines were made. However, these results are not applicable to all settings, especially where the risk of mortality is high such as those with very severe disease or child having severe malnutrition.

INDIACLEN task force on pneumonia states that unless the evidence is more compelling and is replicated to all settings, there is no justification in changing the current practice of hospital admission, detailed assessment, injectable antibiotics and supportive therapy. This study is mainly carried out to compare the efficacy of oral antibiotic against IV antibiotic in our population. If this study proves non-inferiority of oral amoxicillin over parenteral penicillin, safe community level management can increase the number of children benefitted from our care. Hospitalization can lead to many disadvantages like nosocomial infections, increased health care costs, indirect expenses etc. that can be avoided by ambulatory management (2,23).

AIMS AND OBJECTIVES

This study is conducted to compare the efficacy and safety of oral amoxicillin against intravenous ampicillin in children of age 3- 59 months with chest indrawing pneumonia according to revised WHO guidelines.

METHODOLOGY

STUDY DESIGN: Randomized controlled trial-non inferiority design, with allocation concealment and block randomization.

STUDY SETTING: General pediatric wards ofInstitute of child health and hospital for children.

STUDY PERIOD: November 2016- September 2017

STUDY POPULATION:

INCLUSION CRITERIA: All children of age 3-59 months who have chest indrawing pneumonia according to WHO classification.

EXCLUSION CRITERIA:

1. Known cases of immunodeficiency.
2. Asthma.
3. Children who had antibiotics>48 hrs for the current illness.
4. Lower chest retractions responding to nebulisation.
5. H/o cough /difficulty in breathing for more than 2 weeks.
6. Severe acute malnutrition.
7. Those not given consent for the study.

SAMPLE SIZE: 100 (convenient sampling).

MANOEUVRE

The study was commenced after obtaining approval from the Institution Ethical committee. All children of age 3-59 months admitted for chest indrawing pneumonia without any danger signs as classified by WHO were admitted and considered for recruitment. The whole procedure was explained to the parents and consent obtained.

The baseline characteristics of the child like name,age in months, sex were noted. Duration of symptoms of cough and cold, fever, fast breathing, noisy breathing whether present or not, and any other symptoms were also noted. Any past history of admissions, drug intake and any previous surgeries were enquired.

Anthropometric measurements of the child were made. Height of the child is measured using standard methods. The length of the children less than 2 years was measured using an infantometer. The height of the children ≥2 years was measured in stadiometer without shoes and head, shoulders, buttocks and heels touching the board. Weight of the children was measured using an electronic weighing scale. Weight for age, Height for age and Weight for length/height were plotted using WHO growth charts. Children with severe acute malnutrition were excluded from the study. Children with moderate acute malnutrition were included in the study.

The whole procedure was explained to the recruited parents. Clinical data of the children like temperature, heart rate, respiratory rate, presence of

any added sounds were noted at the time of admission. Axillary temperature of the children was recorded at admission using a digital thermometer. Temperature more than 37^0c was taken as fever. Heart rate is auscultated for one full minute. Age- wise cut-off values were used to classify normal heart rate and tachycardia. The child was undressed up to waist and child was seated in non- threatening position (preferably in mother's lap) to count respiratory rate. It was counted by placing hand on the chest and the respiratory movements were counted for one full minute.

Chest indrawing is the inward movement of lower chest wall when the child breathes in and it is a sign of respiratory distress. Both intercostal and subcostal retractions are taken into account. Those children with lower chest retractions responding to bronchodilator nebulization were excluded from the study. The presence of added sounds and type of added sounds (crackles, wheeze, or both) were also documented.

The children were randomized in the ratio of 1:1 using computer generated randomization codes with the block size of 10. Random sequence was generated by one of the co-guides and placed in serially numbered opaque sealed envelopes. The children were assigned to treatment by the principal investigator using consecutive envelopes. The oral group children were given oral amoxicillin 80 mg/kg/day in two divided doses for 5 days and in intravenous group, ampicillin 200 mg/kg/day in three divided doses was given for 5 days. These children were also subjected to blood and radiological investigations based on the unit protocol.

The children were followed up after 48hrs and 5 days for the clinical improvement. Data like temperature, respiratory rate, heart rate, added sounds and persistence of retractions after 48 hours were noted. Any development of danger signs, other new symptoms, adverse reactions to the drug were also recorded. The supportive measures given to the child like antipyretics, nebulization were taken into account. Any detoriation after 48 hours were noted and time taken for the discharge of the study children were documented. All the children were followed up till discharge/ death.

The **primary outcome** of the study is taken as absence of improvement or detoriation in the study children that warrants escalation of antibiotics in either arm at the end of 48 hours of initiation of therapy.

STATISTICAL ANALYSIS

The data from the forms were entered in the excel sheet. Statistical analysis of the data was performed by SPSS software version 21. The primary outcome was measured in both the limbs and expressed as risk ratio and risk difference between the two limbs. Analysis was made to compare the baseline characteristics of two groups and to find predictors of poor outcome of the disease.

RESULTS

A total of 100 children of age 3-59 months with chest indrawing pneumonia were included for the study.

AGE AND GENDER DISTRIBUTION:

Table 5 shows the age and sex distribution of the study population:

AGE	MALE n(%)	FEMALE n(%)	TOTAL n(%)
< 12 MONTHS	24 (24%)	10(10%)	**34(34%)**
1-5 YEARS	37 (37%)	29(29%)	**66(66%)**
TOTAL	**61(61%)**	**39(39%)**	**100(100%)**

Table 5: Age and sex distribution

The median (IQR) age of the study population was 15.5 months. (11-25.5)

Male: Female ratio was 1.56:1.

PRESENTING COMPLAINTS:

Most of the children presented with fever, cough and cold and breathlessness of variable duration. Some children also had other symptoms like vomiting, loose stools and other symptoms.

Mean (SD) duration of cough and cold was 4.86 (1.975) days.

The mean (SD) of fever was 4.47 (2.129) days.

Median (IQR) duration of fast breathing was 2.5 (2-3) days.

None had noisy breathing.

The following figure shows other symptoms seen in the study population:

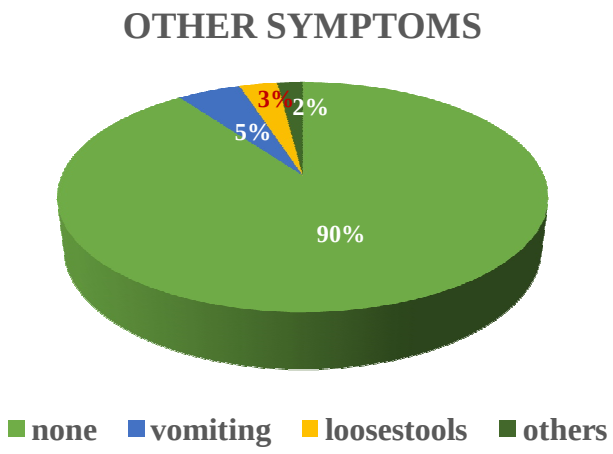

Figure 5: Other symptoms in study population

90% of the study population had no other symptoms. 5% had vomiting of feeds. 3% had loose stools. And 2% had other symptoms. One child presented with simple febrile seizures and the other child had hydrocele.

PAST HISTORY:

Only 3 out of 100 children had a significant past history and had previous hospitalization. One child was admitted for atypical febrile seizures and was on oral phenobarbitone. Another child was aknown case of seizure disorder on oral sodium valproate. One another child was a known case of posterior urethral valve on regular surgical follow up and not on any drugs.

ANTHROPOMETRY:

HEIGHT FOR AGE:

The following pie chart shows height for age of the study population:

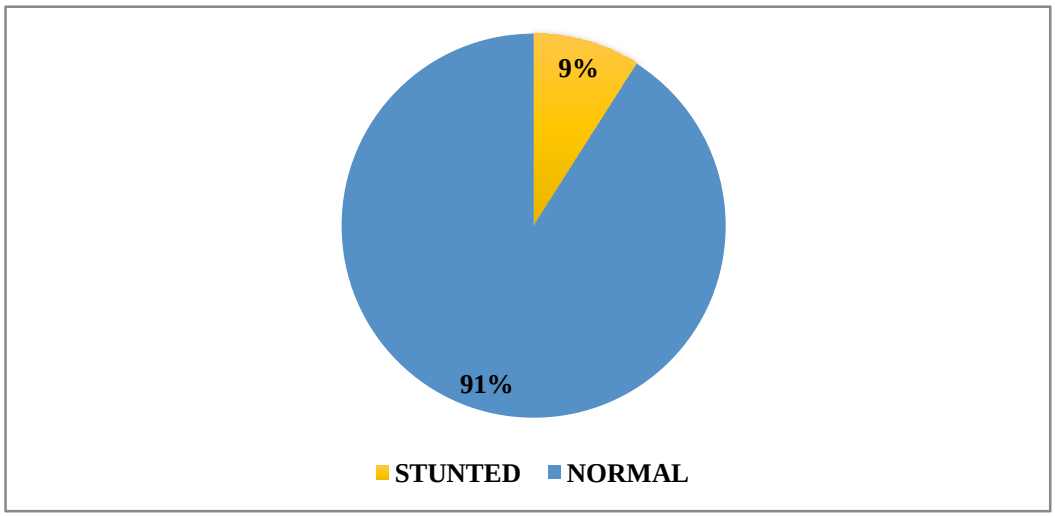

Figure 6: Height for age.

91% of the children had a normal height and 9% of them are stunted for age.

WEIGHT FOR AGE:

The following chart shows the weight for age of the study population:

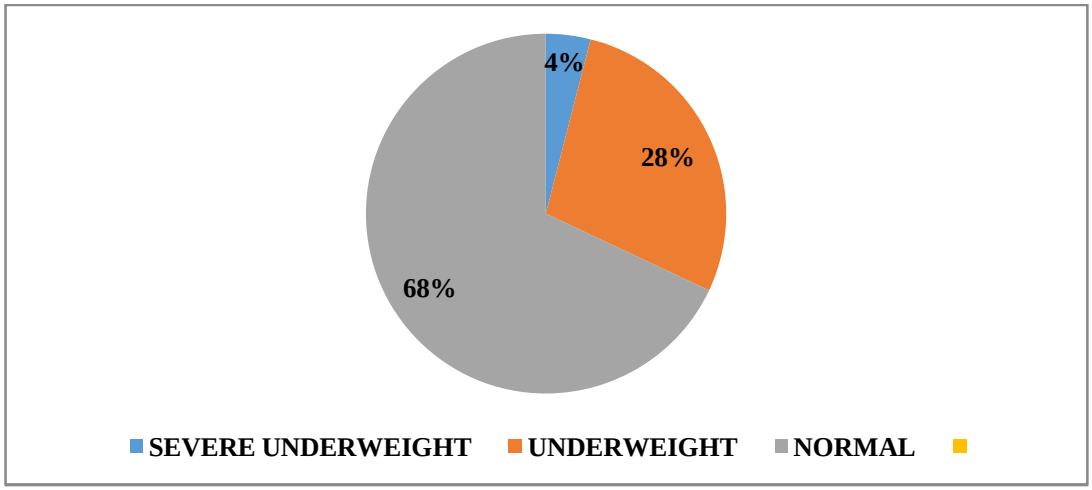

Figure 7: Weight for age

68% of the study population had a normal weight. 28% falls under underweight and 4% of them were severe underweight according to WHO standards.

WEIGHT FOR LENGTH/HEIGHT:

The following chart shows the weight for length distribution of the study population:

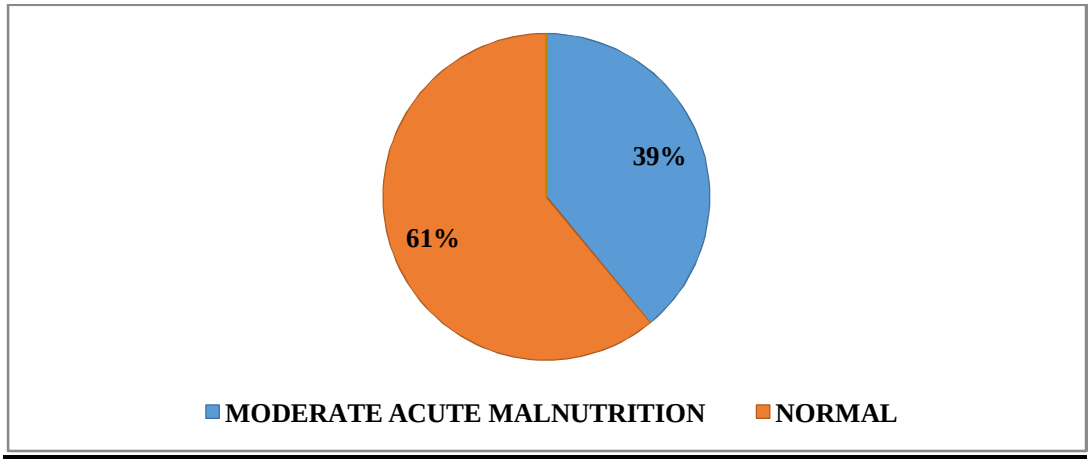

Figure 8: Weight for length/height

Out of 100 study children, 39 children came under moderate acute malnutrition category. 61 children had normal weight for length/height.

CLINICAL DATA ON ADMISSION:

All children had respiratory distress and tachypnea according to their age at the time of admission. The following bar diagram depicts the percentage of children with respiratory distress, normal/ increased heart rate and with / without fever.

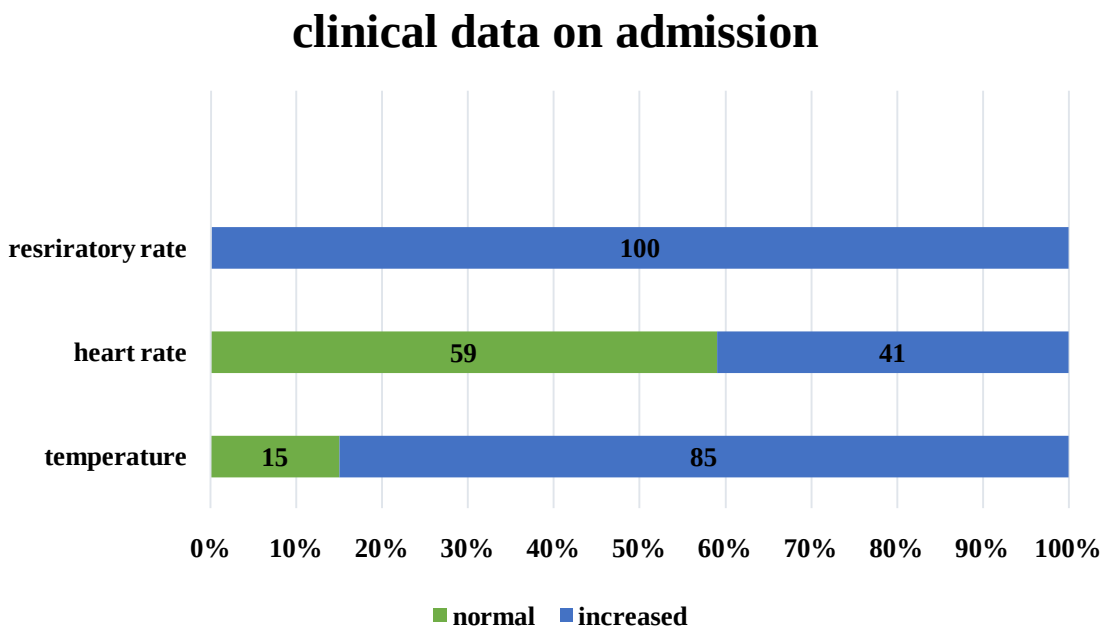

Figure 9: Clinical data on admission(temp, RR, heart rate)

15% of the population had normal temperature. 85% had fever. Of these seven children had very high temperature (>38 c). 59% of children had normal heart rate and 41% had tachycardia. None of the children had bradycardia. All the children had increased respiratory rate on admission.

ADDED SOUNDS:

Presence or absence of added sounds in the form of crackles or wheeze were noted. The following chart shows the percentage of children with crackles/ wheeze/ both.

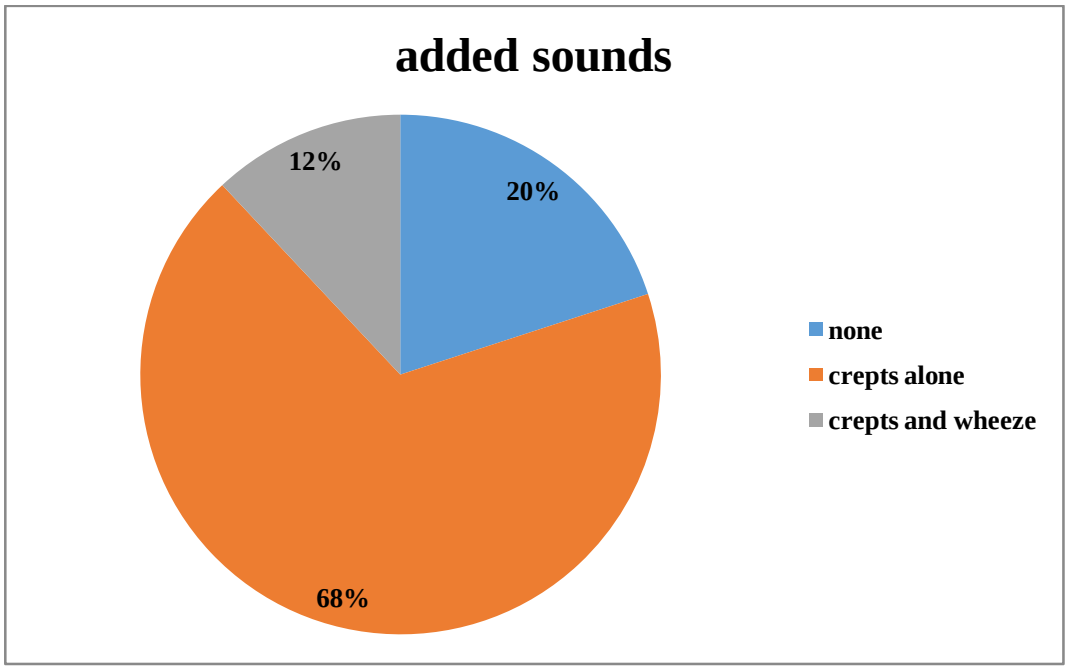

Figure 10: Added sounds at the time of admission

Majority of the children had crackles alone at the time of admission (68%). 20% of the children had no added sounds. 12% of the children had both crackles and wheeze.

INVESTIGATIONS:

XRAY FINDINGS:

28% of the children had no findings in the xray.40% of the children had x-ray finding suggestive of pneumonia (37%- bronchopneumonia, 3%- patchy consolidation). 32% of the children had bilateral hyperinflation.

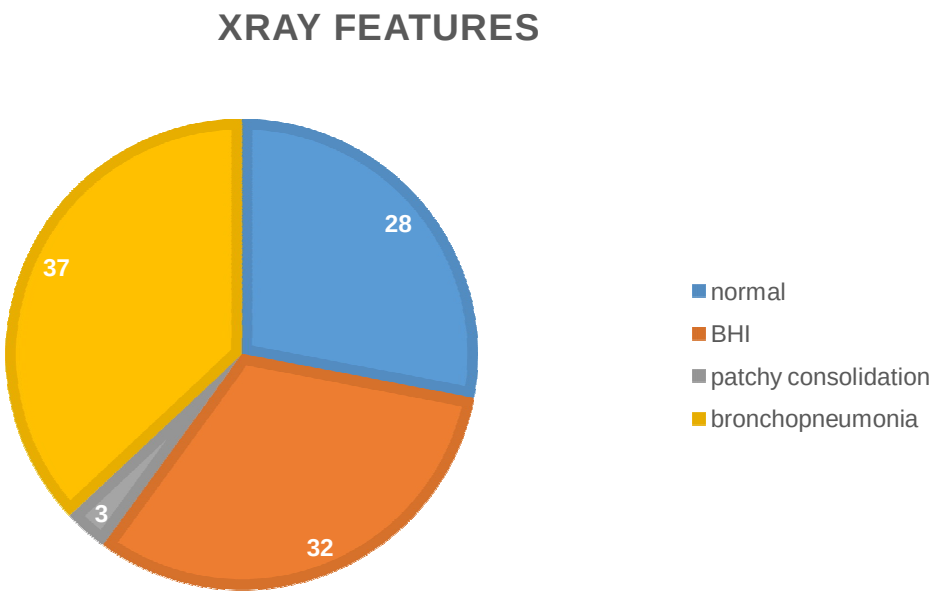

Figure 11: chart showing the X-ray findings

TOTAL AND DIFFERENTIAL COUNT:

Total count was raised in 37% of the children. Among 37% of those with raised counts, 33 children had polymorphonuclear leukocytosis, and 4 children had lymphocytosis.63% of the children had normal counts. The following chart depicts the percentage of children having normal/ raised counts and it also shows, among those with raised counts, whether it is polymorphonuclear leukocytosis or lymphocytosis.

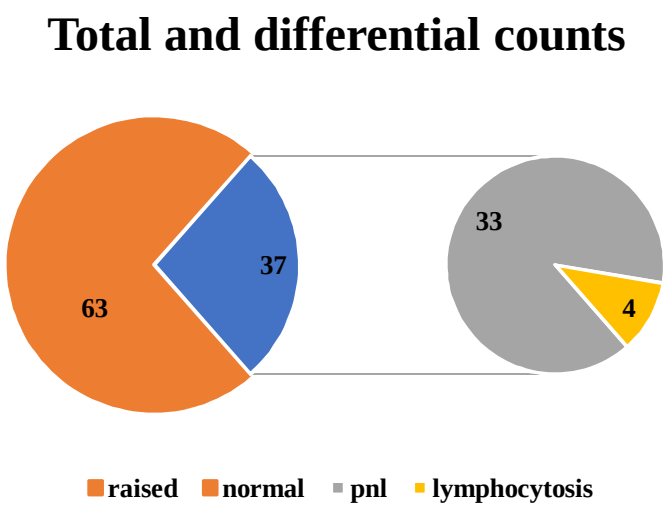

Figure 12: Total and differential count in the study population

C- REACTIVE PROTEIN:

C reactive protein, an acute phase reactant is the marker of inflammation. It indicates the presence or absence of infection. CRP is positive in 78% of the cases and negative in 22%. The following diagram shows the percentage of children in who CRP is positive.

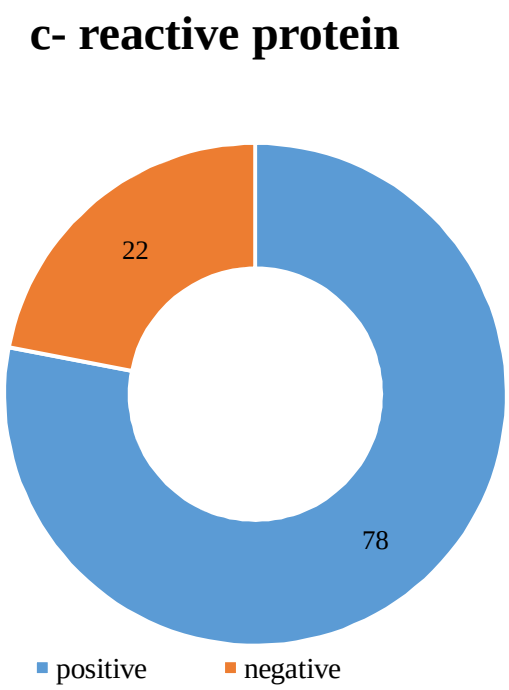

Figure 13: C –reactive protein in the study population

CO INTERVENTIONS:

Most of the children received antipyretics and nebulization as supportive management.68% of the children received only paracetamol. 26% of the children received 3% saline nebulization. 4 children received salbutamol nebulization. Two children received both nebulization and nasal oxygen for supportive management. The bar chart shows the percentage of children who received supportive measures.

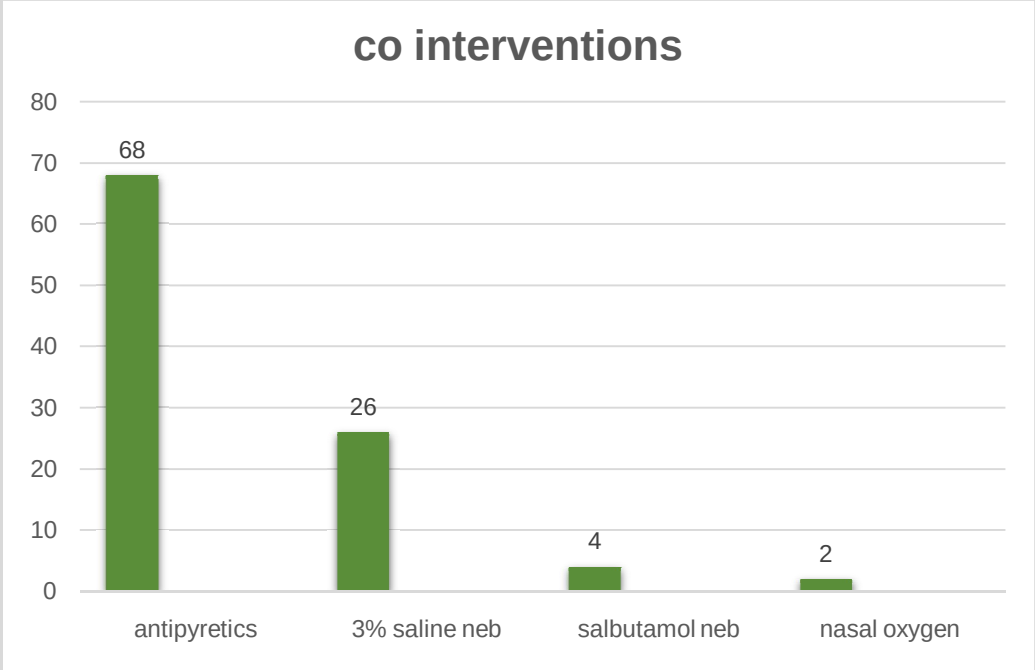

Figure 14: co interventions given to the study population

CLINICAL DATA AFTER 48 HOURS OF ADMISSION:

Only one child left the study before 48 hours whose clinical data could not be collected.

TEMPERATURE:

Most of the children became afebrile at the end of 48 hours. 86 children were afebrile and 13 children continued to have fever spikes. The pie chart depicts the percentage of children with normal/ raised temperature after 48 hours.

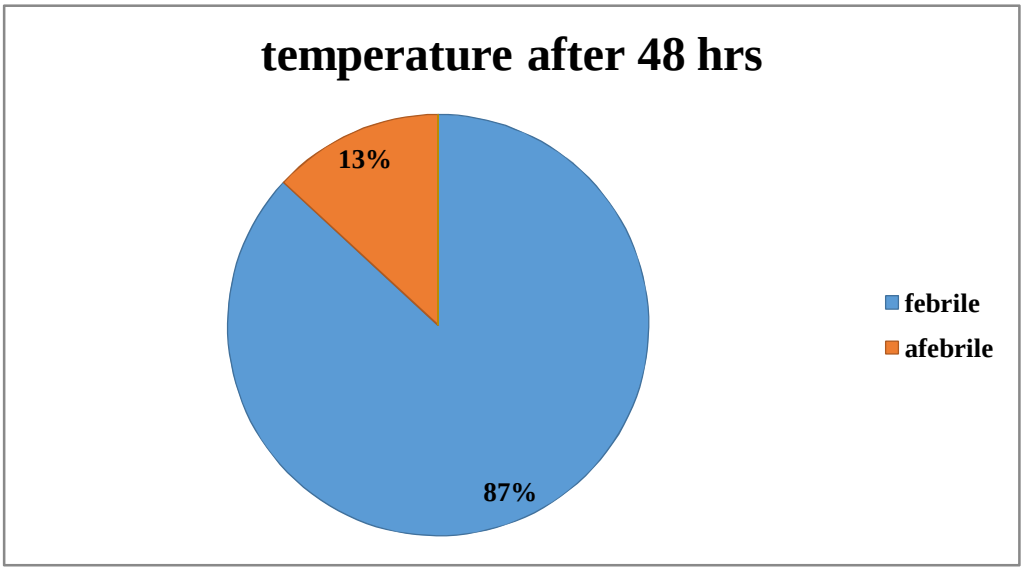

Figure 15: Temperature at the end of 48 hours.

RESPIRATORY RATE:

The respiratory rate should come down at the end of 48 hours. Failure of this indicates treatment failure. In 74 children, who initially had tachypnea, respiratory rate became normal. In 17 children, the RR decreased but doesn't fall in normal range. In 4 children, it remained same. It neither increased nor decreased. In 4 children the respiratory distress worsened with increase in rate. The following bar diagram shows the respiratory rate in children after 48 hours of admission.

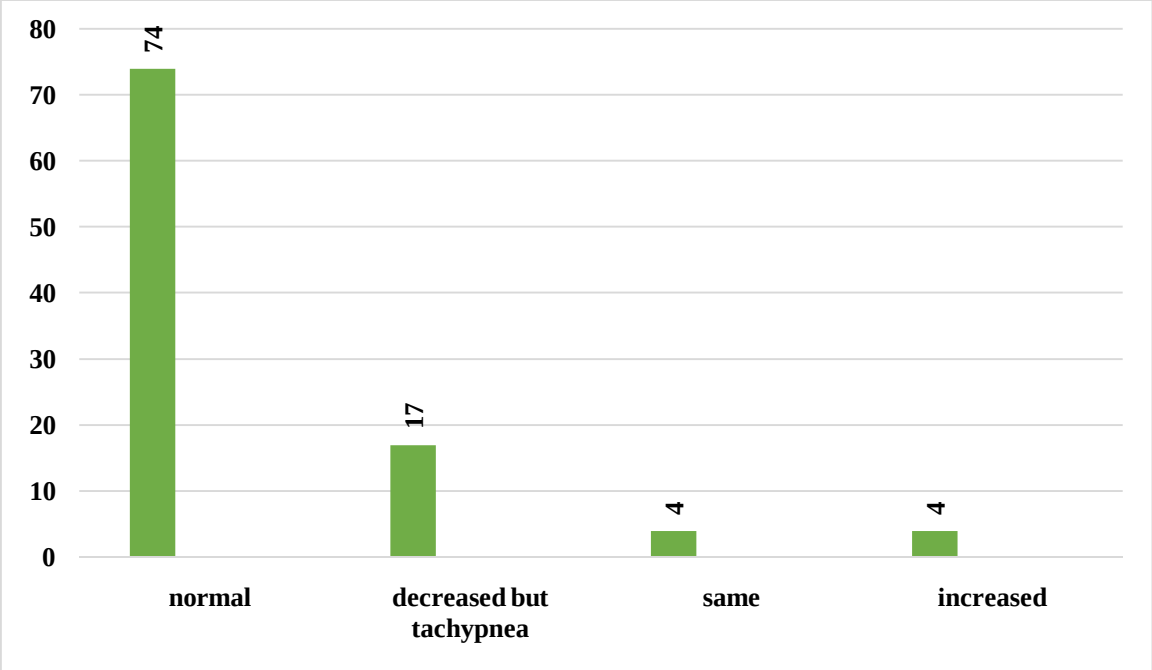

Figure 16: Respiratory rate at the end of 48 hours

HEART RATE:

90 children had normal heart rate and 9 children persisted to have tachycardia. The pie chart shows the percentage of children with normal heart rate and tachycardia.

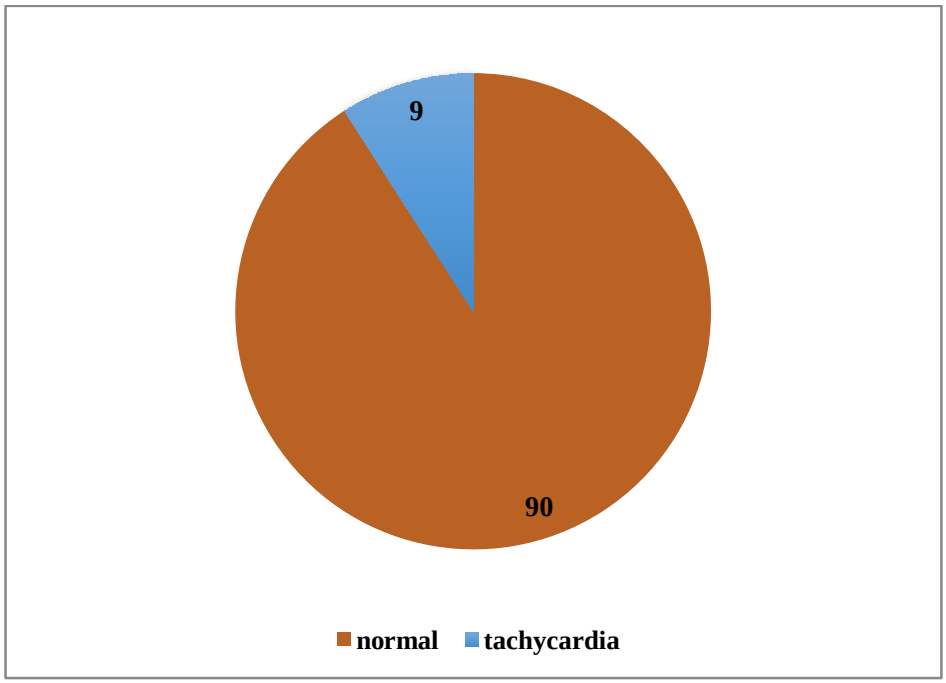

Figure 17: Heart rate at the end of 48 hours.

ADDED SOUNDS AND RETRACTIONS:

82 children did not have any added sounds at the end of 48 hours. 15 children continued to have crackles and 3 children had both crackles and wheeze.78 children had no retractions and 21 had retractions at the end of 48 hours. The clustered bar chart shows the percentage of children in whom retractions persisted and also the type of added sounds that was present at the end of 48 hours.

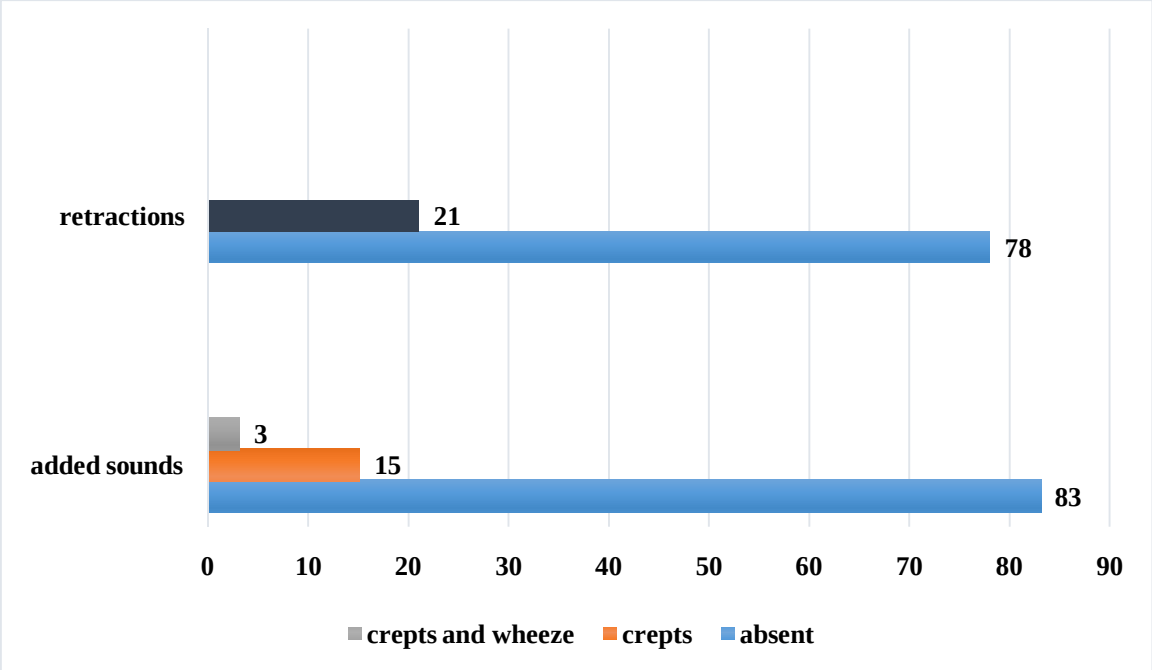

Figure 18: Added sounds and retractions at the end of 48 hours.

OUTCOME OF THE STUDY:

At the end of 48 hours, of the total 99 children who were on follow up, 81 children improved in both limbs and in 18 children treatment was escalated in both the limbs. None of the child expired during the study. This pie chart shows percentage of children who showed improvement and those in whom treatment was escalated.

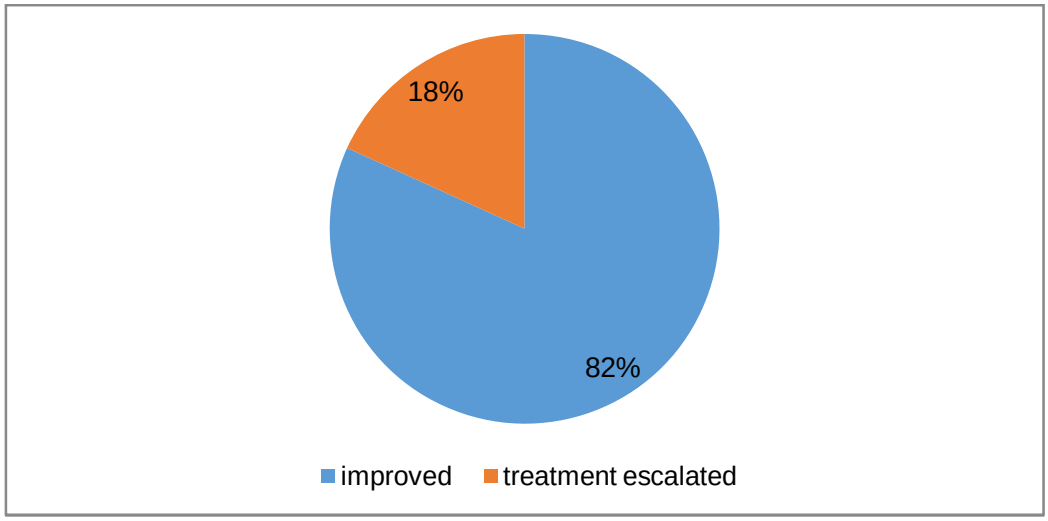

Figure 19: outcome at the end of 48 hours

DETORIATION AFTER 48 HOURS:

2 children detoriated after 48 hours in whom treatment was escalated and 97 children showed no detoriation.

FINAL OUTCOME OF THE STUDY POPULATION:

None of the children recruited for the study expired during the study period. 75 children were successfully discharged at 5 days after admission. 22 children were discharged at around 7-10 days . 3 children left the study before 5 days of which one child left before 48 hours. There was no adverse reactions reported during this study.

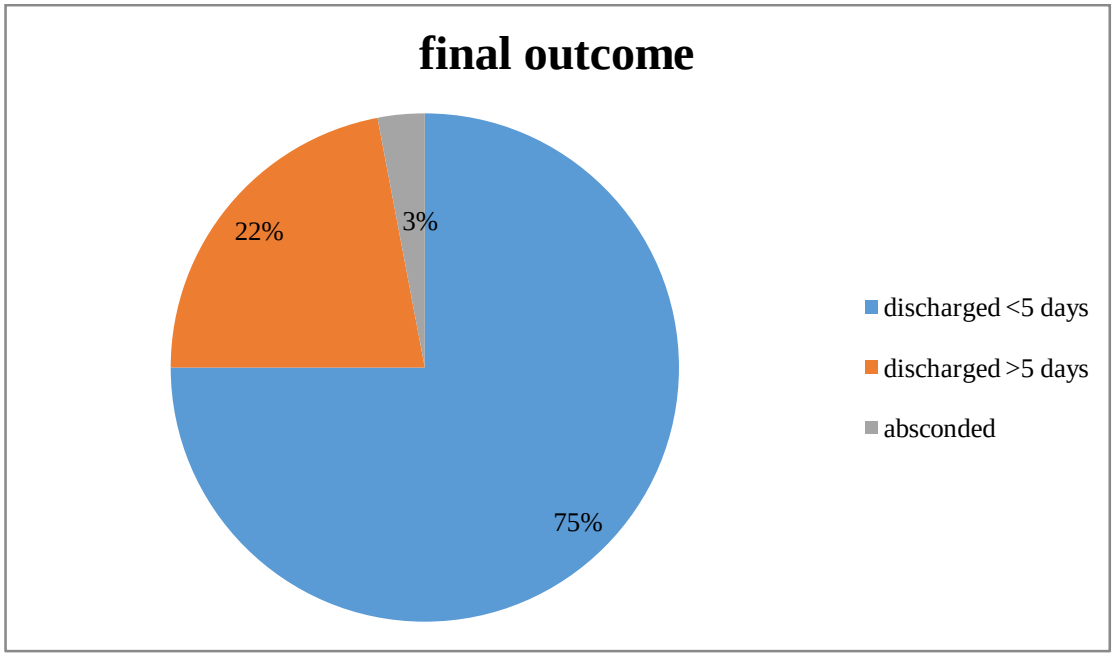

Figure 20: Final outcome of the study

COMPARISON OF BASELINE VARIABLES OF BOTH LIMBS:

Various individual parameters that can influence the outcome of the disease like age of the child, nutritional status, duration of the symptoms like fever, cough and cold, presence of added sounds, Xray findings, co interventions provided for the children in both the limbs are compared to find if there is any significant difference in the baseline characteristics that can alter the outcome of the disease. The following table shows the comparison of baseline characteristics between the two groups:

PARAMETER	ORAL AMOXYCILLIN	IV AMPICILLIN	X^2	P VALUE
INFANCY	18/50	16/50	0.178	0.624
COUGH AND COLD DURATION	4.74(1.498)	4.98(1.964)	0.214	0.624
MODERATE ACUTE MALNUTRITION	23/50	16/50	2.60	0.151
FEVER	42/50	43/50	0.078	1.000
WHEEZE	6/50	6/50	0.0	1.000
CXR pneumonia	22/50	18/50	0.667	0.414
CRP POSITIVITY	339/50	39/50	0.0	1.000
NEBULISATION	14/50	39/50	0.190	0.663

Table 6: comparison of baseline variables

This table clearly shows that there is no significant difference in the baseline characteristics between two limbs.

COMPARISON OF INTERVENTION WITH OUTCOME AT THE END OF 48 HOURS:

Each arm (oral & parenteral) had 50 children in the group. Among the oral amoxycillin group, 1 child left the study before 48 hrs so that outcome cannot be measured in that child.of the total 49 children in oral amoxycillin group, 41 children improved at the end of 48 hours. In 8 children, treatment was escalated to parenteral antibiotic.among 50 children in IV ampicillin group, 40 children improved with treatment and in 10 children, it is escalated to higher antibiotics.The treatment failure is 16.3% (8 out of 49) in oral amoxycillin group and 20.3%(10 out of 50) in IV ampicillin group. The table 7 compares the outcome of the disease in both the limbs which is the primary measure of this study.

		ORAL AMOXYCILLIN N(%)	INTRAVENOUS AMPICILLIN N(%)	TOTAL N(%)
OUTCOME AT THE END OF 48 HOURS	**IMPROVED**	41(41%)	40(40%)	81(81%)
	TREATMENT ESCALATED	8(8%)	10(10%)	18(18%)
	TOTAL	49(49%)	50(50%)	99(99%)

Table 7: Comparison of outcome at the end of 48 hours in both limbs

The results can be interpreted in the form of **Risk difference** between two limbs.

(8/49) - (10/50)= 0.1632-0.2000= - 0.0368.

Risk ratio is calculated as (8/49) / (10/50)=0.1632/0.2000= 0.8163. 95% CI (0.3517-1.8949).

Chi square tests were performed on these data to find the significance in failure rate of these two limbs.The $\mathbf{x^2}$value is **0.472** and **p value is 0.636** which is not significant.

PREDICTORS OF POOR OUTCOME AFTER 48 HOURS IN CHILDREN:

Analysis were done to identify the individual parameters that can affect the outcome of the disease in the children. Age of the child, duration of symptoms, CXR findings, presence of wheeze in the child, nutritional status were taken into account .

AGE OF THE CHILDREN:

This study was carried out in children from age 3 months to 5 years. For analysis, they were grouped as infants (3-11 months) and non infants (>12 months) because in various trials conducted before, infancy is an important predictor in treatment failure. In the following table , data were analysed to find whether age of the child affects the outcome of the disease.

		IMPROVED	TREATMENT ESCALATED	TOTAL
AGE OF THE CHILDREN	**3-11 months**	26	8	34
	>12 months	55	10	65
	TOTAL	81	18	99

$X^2 = 0.995$; $p = 0.318$

Table 8: Age of the children on the outcome at 48 hours

Only 34% of the study population belonged too age 3-11 months. Of these, 26 children improved with antibiotics and only in 8 children the treatment was escalated too higher antibiotics in their respective arms. The **X^2 value is 0.995 and the p value is 0.318** which is not significant.

DURATION OF SYMPTOMS:

The duration of cough and cold and respiratory distress during the time of admissions are analysed to predict their influence on the outcome of the children.

The mean duration of illness in those who improved and in those treatment escalated were calculated.

OUTCOME AT 48 HOURS	NUMBER OF CHILDREN	MEAN	STD.DEVIATION	STD.ERROR MEAN
IMPROVED	81	4.70	1.993	0.215
TREATMENT ESCALATED	18	5.44	2.093	0.493

Table 9: Duration of symptoms on outcome at 48 hours

Totally 81 children improved and in 18 children treatment were escalated. The mean duration of symptoms was calculated. It was 4.70 in improved group and 5.44 days in children. The **p value is 0.957 which is not significant.**

NUTRITIONAL STATUS:

This trial excluded the children with severe acute malnutrition as they must be admitted and started on intravenous antibiotics irrespective of the severity of illness. So, the study population was classified as those with moderate acute malnutrition and those who had normal weight for length to analyse their predictability in treatment failure.

		Improved	Treatment escalated	Total
Nutritional status	**Moderate acute malnutrition**	30	9	39
	Normal	51	9	60
	Total	81	18	99

$X^2=1.037$; $p = 0.309$

Table 10: Nutritional status on outcome at 48 hours.

This table shows that , of the total 39 chiildren who had moderate acute malnutrition, 30 children and in only 9 children treatment was escalated.In normal children also, 9 children did not respond to treatment. The **X^2 value is 1.037 and p value is 0.309** which is not significant. Thus, nutritional status of the child does not have any significant influence over the disease outcome.

DURATION OF FEVER:

The duration of fever was taken into account because in previous studies, persistance of fever beyond a period of 6 days became a important predictor in the poor outcome in those children.

	At the end of 48 hours	Improved	Treatent escalated	Total
Fever	**Present**	12	2	14
	Absent	69	16	85
	Total	81	18	99

X^2 =0.166 ; p =0.683

Table 11: Duration of fever on outcome at 48 hours

Fever persisted in 14 children at the end of 48 hours. Of those, only in 2 children treatment were escalated and 12 children improved with antibiotics. 85 children did not have fever at the end of 48 hours. Eventhough fever subsided, in 16 children, treatment was escalated was various other reasons, mainly persistence of retractions. The **X^2 value is 0.166 and p value is 0.683** which is not significant.Thus duration of fever does not alter the outcome of the disease.

PRESENCE OF WHEEZE:

Most of the children included in the study had only crackles at the time of admission. But some children presented with both crackles and wheeze. Analysis was done to find out whether presence of wheeze affects the outcome at the end of 48 hours.

		IMPROVED	TREATMENT ESCALATED	TOTAL
WHEEZE	**PRESENT**	7	5	12
	ABSENT	74	13	87
	TOTAL	81	18	99

$X^2 = 5.063$; $p = 0.024$

Table 12: Presence of wheeze on the outcome at 48 hours.

Totally 12 children recruited had both crackles and wheeze. Of these, 7 children improved with treatment and in 5 children treatment were escalated. The **X^2 value is 5.063 amd p value is 0.024 which is significant.** so, presence of wheeze in children admitted for pneumonia is a predictor of poor outcome in our population.

CXR FINDINGS:

CXR findings are not necessary for the initiation of therapy at the community level. Presence of bronchopneumonia and patchy consolidation were taken as significant findings. Those children with CXR positive findings were analysed for the outcome.

	Features suggestive of pneumonia	**Improved**	**Treatment escalated**	**Total**
CXR	**Present**	27	13	40
	Absent	54	5	59
	Total	81	18	99

$X^2 = 9.250$; $p = 0.002$

Table 13: CXR findinds on the outcome at the end of 48 hours.

This table shows that, of the total 40 children who had CXR findings suggestive of pneumonia, in 13 children treatment was escalated to higher antibiotics, whereas in those who did not have cxr features, only in 5 children treatment was escalated. The **X^2 value is 9.250 and p value is 0.002 which is significant.** Thus this study shows that, those children with CXR findings take longer time to improve than those with who did not have CXR findings.

To summarize,the following table tries to find the predictors of poor outcome of the disease.

PARAMETER	CATEGORY	IMPROVED	TREATMENT ESCALATED	X^2	P VALUE
INFANCY	INFANTS	26/34	8/34	0.995	0.318
	>1 YEAR	55/65	10/65		
COUGH AND COLD DURATION		4.70(1.933)	5.44(2.093)	0.003	0.957
NUTRITION	MAM	30/39	9/39	1.037	0.309
	NORMAL	51/60	9/60		
FEVER	YES	12/14	2/14	0.166	0.683
	NO	69/85	16/85		
WHEEZE	YES	7/12	5/12	5.063	**0.024**
	NO	74/87	13/87		
CXR PNEUMONIA	POSITIVE	27/40	13/40	9.250	**0.002**
	NEGATIVE	54/59	5/59		

Table 14: Predictors of poor outcome of the disease

This table shows that age, symptoms duration, nutritional status and fever does not influence the outcome of the disease.Only presence of wheeze in children with pneumonia and CXR findings suggestive of pneumonia significantly affects the outcome of pneumonia at the end of 48 hours.

DISCUSSION

Our study revealed that there is no significant difference in the treatment failure rate in children of age 3-59 months with chest indrawing pneumonia where one group of children were treated with high dose of oral amoxycillin and another group treated with parenteral ampicillin. Thus this trial proved the non inferiority of oral amoxycillin over parenteral ampicillin and thus can be used in the ambulatory basis for the management of chest indrawing pneumonia.

The treatment failure rate in oral amoxycillin group is 16.3% and in intravenous ampicillin group is 20.3% with minimum risk difference between two groups.The most common reason for the escalation to higher antibiotics was failure of improvement of symptoms rather than worsening of symptoms or appearance of danger signs in our study. The baseline characteristics were comparable in both the limbs.The presence of wheeze in the children at the time of admission and CXR features suggestive of pneumonia were the factors that significantly affected the outcome of the children in both the arms. There was no deaths/ adverse events reported during the study period.

The primary outcome of our study was in accordance with the previous trials done similarly comparing the oralantibiotics with parenteral antibiotics in pneumonia.But the failure rates were high when compared to the previous trials because the sample size was low and the primary outcome was measured after

48 hours whereas in pervious international trials, in most trials, the primary outcome was measured at the end of 6 days.

A meta analysis is conducted compiling the trials from different regions of the world that led to the change in the treatment protocol for children with chest indrawing pneumonia by WHO (Addo Yobo et al, Hazir et al, Campbell et al, Agweyu et al).Most previous trials done compared oral amoxicillin and parenteral penicillin. Only one trial used cotrimoxazole and procaine penicillin(27). However, the results were same irrespective of the group of antibiotic used. All the trials proved the equivalency of oral antibiotic and parenteral antibiotics.

All the children were admitted in the hospital and randomized into oral and parenteral group in our study. In the meta- analysis, most of the trials were done partly / fully in hospital and only one trial was done completely as ambulatory basis(27). In study conducted by Addo Yobo et al, both the groups were hospitalized. But, the outcome was not affected in any trials because of hospitalization.There were ther similar studies done in Pakistan that concluded that community level management is equivalent to hospital management.

In the study conducted in India , nine pediatric centers were included in the study to study the equivalence of oral and parenteral treatment and also cost analysis in both limbs. Treatment failure were similar in both groups and ambulatory management was cost effective than hospitalization (direct and indirect health care costs). Cost analysis was not done in our study. (3)

In most of the trials done before, young infants (3-11 months) , presence of very fast breathing were the poor predictors of outcome in both the limbs. In our study, both infancy and respiratory rate were not significant in predicting the outcome of the disease. This discrepancy can be due to the sample size as only 100 children were recruited for convenient sampling. Of the total study population , only 34 children belonged to age of 3-11 months. A larger sample size could have led to more number of infants included in the study.

Only one study byAddo Yobo et al (25) considered the nutritional status of the children included in the study. But it was not a poor predictor of outcome. This is in concordance with our study. Children with / without malnutrition responded equally to the treatment.

The presence of wheeze at the time of admission was a significant predictor of poor outcome in our study . Only one study done in the past,considered the significance of presence of wheeze at admission but it was not a predictor of poor outcome (29). Wheeze when present is mostly a feature of viral pneumonia and this could be the reason for delay in improvement in these children.

Those children with Xray findings consistent with pneumonia (patchy consolidation and bronchopneumonia) took longer period for resolution of the disease compared to those in whom CXR was normal. WHO does not include CXR findings to classify pneumonia. None of the studies included in the meta-

analysis considered laboratory/ radiological findings in the study. Previously , a study was conducted in Botswana in a tertiary center to predict the outcome in children with CXR positive pneumonia. That study showed that CXR finding consistent with pneumonia was an independent predictor of poor outcome in the children. Similar study done in India (Himachal pradesh) shows that time for defervescence for outcome measures were similar with consolidation, interstitial pneumonia or normal xrays. However, the length of stay was prolonged in these children with positive CXR findings. This is consistent with our study. Most children with positive CXR findings were discharged around 7 -10 days when compared to those children with normal Xrays who were discharged at 5 days.(38)

Amoxicillin and ampicillin belongs to same group of penicillins (aminopenicillin). Amoxicillin have higher peak serum concentrations , larger ‘ area under the curve’ and greater urinary excretion than ampicillin (39). Half lives of both amoxicillin and ampicillin are same. However , studies shows that high doses of amoxicillin when given orally reaches same peak serum concentration obtained by giving same dose of ampicillin intramuscularly. Thus amoxicillin in high doses can be used for certain infections that are treated with parenteral penicillin. (42)

Thus this trial showed that high doses of amoxicillin can be used in place of intravenous ampicillin in the treatment of chest indrawing pneumonia in our population. This will minimize the hospital acquired infections , direct and indirect costs spent by the people for hospital admissions.

STUDY LIMITATIONS:

- The main limitation of the study is the sample size. Only 50 children in each arm were recruited as convenient sampling. Whether the results can be applicable to the entire population is not known.
- The feeding pattern of the recruited children were not taken into account.Previous studies have proved the benefit of breastfeeding for faster recovery.

SUMMARY

- Oral amoxycillin in not inferior to parenteral ampicillin in the treatment of children of age 3-59 months with chest indrawing pneumonia according to WHO guidelines.
- The baseline characteristics of the children included does not differ significantly in both arms. So, both the groups were comparablewith respect to all characteristics.
- Presence of wheeze at the time of enrolment not responding to salbutamol nebulisation and CXR findings suggestive of bronchopneumonia were the predictors of poor outcome in these children with pneumonia.

CONCLUSION:

Oral amoxycillin in the dose of 80 mg/kg/day in two divided doses for 5 days is equally efficacious and can be safely used in children having chest indrawing pneumonia according to WHO clasification of age 3-59 months in the community level instead of hospitalisation and parenteral ampicillin.

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DATA COLLECTION FORM

IDENTIFICATION

l. Study Id :

2. Name :

DEMOGRAPHIC CHARACTERISTICS

3. Age a) DOB:_____

b) Age in months: _____

c) Category: 1) 3-12 months 2)13-36 months 3) 37-60 months

4. Sex : 1) Male 2) Female 3) Others

PRESENT HISTORY

5. Cough & cold duration - _____

6. Fever – 1) Yes 2) No If YES, duration - _____

7. Fast breathing 1) Noticed 2) Not noticed If yes, duration- _____

8. Noisy breathing – 1) Yes 2) No If yes, duration _____

9. Any other symptom -1)no 2) vomiting of feeds 3) loose stools 4)others

PAST MEDICAL HISTORY

10. Pre-existing illness – 1) Yes 2) No If YES specify - _____

11. Hospitalisation in past – 1) Yes 2) No If yes, reason- _____

12. On any medication – 1) Yes 2) No If YES, specify _____

ANTHROPOMETRY

13. Height/length- in cm ☐

1) <-3 z score **2)** -3 to -2 3**)** -2 to +3 4) >+3 z score

14. Weight- ☐ kg

1**)**<-3z score **2)** -3to -2 **3)** -2 to +1 4) > +1 z score

15. Weight for length- 1)<-3 z score 2) -3 to -2 z score 3) -2 to +1

4) +1 to +2 5) +2 to +3 6) > +3 z score

CLINICAL DATA AT ADMISSION:

16. Temperature: 1) <36.5°C 2) 36.5-38 °C 3) >38°C

17. Respiratory rate (per minute): _____

1) bradypnea 2) normal 3) tachypnea

18. Heart rate (per minute): _____1) bradycardia 2) normal 3) tachycardia

19. Added sounds – 1) None 2) creps alone 3) creps and wheeze

INVESTIGATIONS:

20. CXR – 1) Normal 2) BHI 3) Patchy consolidation

4) Bronchopneumonia 5) Others

21. Total count – 1) Normal 2) Raised

If raised 1) Polymorphonuclear leucocytosis 2) Lymphocytosis

22. CRP – 1) Negative 2) Positive

23. Any other abnormal investigation - _____

24. *TYPE OF INTERVENTION*: 1) ORAL 2) PARENTERAL

25.co interventions: 1) antipyretics 2) saline neb 3) salb neb 4) nasal o2

26. any co morbid illness 1) yes 2) no

27.any detoriation before 24 hours? 1)yes 2) no

CLINICAL DATA AFTER 48 HOURS OF ADMISSION:

25. Temperature- 1) <36.5 °C 2) 36.5-38°C 3)> 38°C

26. Respiratory rate (per minute): _____

1) Normal 2) Decreased, but tachypneic 3) Same

4) Increased

27. Heart rate (per minute): _____

1) Normal 2) Tachycardia

28. Added sounds – 1) None 2) creps alone 3) creps and wheeze

29. Chest retractions- 1) Absent 2) Present

30. Any new symptom/sign/complication – 1) Yes 2) No

If YES, then _____

OUTCOME:

31. At the end of 48 hours – 1) Improved 2) Treatment escalated

a) no improvement b) appearance of danger signs

3) Expired- Cause of death and duration of stay

32. Any deterioration after 48 hours 1) Yes 2) No If YES, cause and timing _____

33. Final outcome – 1) Discharged≤ 5 days 2) discharged >5 days 3) left the study

4) Died

தகவல் படிவம்

ஆய்விடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

முதன்மை ஆராய்ச்சியாளர் : மரு.ம.கோகிலவாணி

பங்கு பெறுபவரின் பெயர் : வயது : பாலினம் :

மருத்துவமனை எண் :-

ஆய்வு தலைப்பு : 3-59 மாதங்கள் வயதுள்ள குழந்தைக்கு ஏற்படும் மார்பு உன்னிக்கும் வகை நிமோனியாவில் வாய்வழியாக அமாக்சிசிலினும் சிரைவழியாக தரப்படும் ஆம்பிசிலின் மருந்தின் தன்மைகளை ஒப்பிடுதல்.

செய்முறை

3-59 மாதங்கள் உள்ள குழந்தைகள் தேர்ந்தெடுக்கப்பட்டு இரு குழுக்களாக பிரிக்கப்படுவர். அதில் ஒரு குழுவிற்கு வாய்வழியாக ஆமாக்சிசிலினும், சிரைவழியாக ஆம்பிசிலின் மருந்தும் கொடுத்து அவற்றின் தன்மைகளை ஒப்பிடுதல்.

ஆய்வில் பங்கேற்க மறுத்தால்?

இந்த ஆய்வில் பங்கேற்பது முற்றிலும் உங்களது சொந்த விருப்பமே. தாங்கள் எப்போது வேண்டுமானாலும் இவ்வாய்ச்சியிலிருந்து விலகி கொள்ளலாம். தாங்கள் விலகி கொள்வதால் உங்கள் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்தவித மாற்றமோ, பாதிப்போ இருக்காது.

பங்கேற்பதின் இலாப மற்றும் நஷ்டங்கள்:-

இந்த ஆய்வில் இருந்து பெறப்படும் தகவல்கள், நம் நாட்டை நோயில்லாத நாடாக மாற்ற உபயோகப்படும். இவ்வாறு நாட்டின் வளர்ச்சியில் பங்கேற்ற பெருமை உங்களையும், உங்கள் குழந்தையையும் சேரும்.

இரகசியத் தன்மை:-

இந்த ஆய்வைப் பற்றி மேலும் தகவல் அறிய தொடர்பு கொள்ள வேண்டிய நபர்

முதன் ஆராய்ச்சியாளர் : மரு.ம.கோவிலவாணி

கைபேசி எண் : 9488563186

முகவரி : இரண்டாம் ஆண்டு முதுநிலை மருத்துவமனை அரசு குழந்தைகள் மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

தேதி :

இடம் :

பெற்றோரின் கையொப்பம்

ஒப்புதல் படிவம்

ஆய்விடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

முதன்மை ஆராய்ச்சியாளர் : மரு.ம.கோகிலவாணி

பங்கு பெறுபவரின் பெயர் : வயது : பாலினம் :

மருத்துவமனை எண் :-

ஆய்வு தலைப்பு : 3-59 மாதங்கள் வயதுள்ள குழந்தைக்கு ஏற்படும் மார்பு உன்னிக்கும் வகை நிமோனியாவில் வாய்வழியாக அமாக்சிசிலினும் சிரைவழியாக தரப்படும் ஆம்பிசிலின் மருந்தின் தன்மைகளை ஒப்பிடுதல்.

1. எனக்கு தரப்பட்ட ஆராய்ச்சியில் பங்கு பெறுவோர்க்கான தகவல் படிவத்தை முழுவதுமாக படித்து புரிந்து கொண்டேன்.
2. ஆராய்ச்சியின் தன்மை முழுவதுமாகவும், விரிவாகவும் எடுத்துரைக்கப்பட்டது. எனது கேள்விகளுக்கு விடையளிக்கப்பட்டது.
3. ஆய்வாளர் எனது உரிமைகளையும், பொறுப்புகளையும் நன்கு விளக்கினார்.
4. நான் எனது குழந்தை, ஆய்வாளருக்கு முழு ஒத்துழைப்பு கொடுக்கவும், பரிசோதனை செய்து கொள்ளவும் அனுமதிக்கிறேன்.
5. எனது குழந்தை ஆராய்ச்சியில் பங்கேற்பதால் ஏற்படும் சாதக பாதகங்கள் விளக்கப்பட்டன.
6. நான் எப்பொழுது வேண்டுமானாலும் எனது குழந்தையை இந்த அந்த ஆராய்ச்சியிலிருந்து விளக்கிக் கொள்ளலாம் என்று எனக்கு எடுத்துரைக்கப்பட்டது.
7. இந்த ஆய்வின் என் குழந்தையிடமிருந்து பெறப்படும் மருத்துவ தகவலை ஆய்விதழிலோ, கருத்தரங்கிலோ வெளியிடுவதில் எனக்கு எந்தவித ஆட்சேபனையும் இல்லை.
8. அவ்வாறு வெளியிடப்படும் போது என் குழந்தையின் அடையாளங்கள் வெளியிடப்படமாட்டாது என எனக்கு உறுதியளிக்கப்படுகிறது.
9. எனக்கு இந்த ஆராய்ச்சி குறித்து எதுவும் சந்தேகம் இருந்தால் உடனே ஆராய்ச்சியாளரைக் கேட்டு தெளிப்படுத்திக் கொள்ளலாம் என தெரிவிக்கப்பட்டது.

10. இந்த ஒப்புதல் படிவத்தில் கையொப்பமிடுவதின் மூலம் இந்த படிவத்தில் உள்ளவை யாவும் எனக்கு தெளிவாக எடுத்துரைக்கப்பட்டு அதை நான் நன்கு புரிந்து கொண்டேன் என தெரிவித்துக் கொள்கிறேன்.

குழந்தையின் பெற்றோர்/பாதுகாவலர்

பெயர் :_____ கையொப்பம் :

தேதி :

ஆராய்ச்சியாளர்

பெயர் :_____ கையொப்பம் :

தேதி :

சாட்சி

பெயர் :_____ கையொப்பம் :

தேதி :