Introduction

Worldwide, pneumonia is the leading cause of pediatric morbidity and mortality. It is estimated that pneumonia is responsible for more than two millions deaths each year in children less than five years age **(Igor Rudan et al.,2008; Bhatnagar and natchu,2004).**

In low-income countries,undernutrition is associated with greater severity of pneumonia, a longer duration of illness and an increased case fatality rate **(Michael Hambidge., 2006; Ugwuja et al.,2007).**

Approximately 95% of the pneumonia related-deaths occur in developing countries and the youngest age group have the highest risk of death (**kumar et al.,2004**).

Of the micronuteients zinc plays a critical role in the development and maintenance of host defenses against infectious diseases (**Ken Brown et al.,2003;Peter Va,2006**).

Mild to moderate zinc defeciency is common in several developing countries because the commonly consumbed staple foods have low zinc contents and are rich in phytate,which inhibit the absorption and utilization of zinc (**Shankar and Prasad,1998).**

Zinc defeciency was shown to impair cellular mediator of innate immunity such as phagocytosis,natural killer cell activity,and the generation of oxidative burst. This is of special importance in populations in which insufficient intake of these nutrients is prevalent in low-and-middle income countries (**Wintergerst et al.,2006).**

Zinc deficiency results in enhanced oxidative damage in the airways by causing infiltration of inflammatory cells. When zinc deficiency occurs in conjunction with acute lung injury or asthma, a more intense inflammation is produced **(Zalewski et al., 2006)**

Aim of the Work

This study was carried out to assess the zinc level in children with severe pneumonia.

PART I: PNEUMONIA

DEFINITIONS:

Pneumonia: Inflammation of the parenchyma of the lungs.

Community Acquired Pneumonia (CAP):Pneumonia that has been acquired in the community in a patient who has not been hospitalized within 14 days prior to the onset of symptoms (**Bartlett et al., 2000**).

Hospital-acquired pneumonia (Nosocomial pneumonia): A respiratory infection developing more than 48h after hospital admission (**Eriksen et al 2004**).

EPIDEMIOLOGY:

Pneumonia is the most common cause of morbidity and mortality in young children worldwide (**Samransamruajkit et al., 2008**).Co-morbid conditions, especially malnutrition, measles or immunosuppressant increase the risk of mortality from pneumonia (**Black el al.. 2003**). Despite major advances in our understanding of the burden and epidemiology of childhood acute respiratory infections, almost two million children still die from pneumonia each year accounting for 20% of deaths in children aged under 5 years globally. Accurate figures are difficult to obtain but the estimated incidence of pneumonia is 151 million new cases a year, and of these, some 11-20 million (7-13%) are severe enough to require hospitalization. These composite figures do not reflect the tremendous inequity both between and within countries, with the bulk of pneumonia deaths affecting the poor with limited access to services (**Bhutta, 2006**).

In North America, the annual incidence of pneumonia in children younger than 5 years is 30 to 45 cases per 1000; in children aged 5 years and older, the annual incidence is 16 to

22 case per 1000. In developing countries which account for more than 95% episodes of clinical pneumonia worldwide, researchers estimate that more than 150 million new cases occur annually in children younger than 5 years **(Sandora et al, 2005).** Three quarters of all pneumonia episodes worldwide among children under five years occur in just 15 countries.

Table (1): 15 countries accounting for three quarters of childhood pneumonia cases worldwide:

India	44 million
China	18 million
Nigeria	7 million
Pakistan	7 million
Bangladesh	6 million
Indonesia	6 million
Brazil	4 million
Ethiopia	4 million
Congo. Democratic Republic of the Philippines	3 million
Afghanistan	2 million
Egypt	2 million
Mexico	2 million
Sudan	2 million
Viet Nam	2 million
Total	113 million

(UNICEF/WHO, 2006)

In 2006. there was a substantial increase in international awareness about pneumonia, helped by the publication of a report by the United Nations Children's Fund (UNICEF) and WHO **(Greenwood et al.. 2007).** The report examines the epidemiological evidence on the burden and distribution of pneumonia and assesses current levels of treatment and prevention. The result are sobering: Only about 1 in 5 caregivers knows the danger signs of pneumonia;only about hallf of children sick with pneumonia receive appropriated medical care, and less than 20 per cent of children with

pneumonia receive antibiotics; the recommended treatment **(UNICEF/WHO, 2006).**

PREDISPOSING FACTORS:

Several risk factors increase the incidence or severity of pneumonia in children: prematurity, malnutrition, low socioeconomic status, .passive exposure to smoke and attendance at day-care centers (**Wang et al., 1995**). Underlying disease, especially that affecting the cardiopulmonary, immune or nervous systems, also increases the risk of severe pneumonia. In one pediatric study, the most common of underlying predisposing factors was aspiration secondary to oropharyngeal muscular incoordination (e.g.. in cerebral palsy).

Other identified illnesses included immune disorders (generally related to malignancy or abnormalities of the humoral immune system, including HIV infection), congenital heart disease, asthma, congenital or acquired anatomic abnormalities (e.g. tracheoesophageal fistula), gastro esophageal reflux and sickle cell anemia (**Owayed et al., 2000**).Patients with endotracheal tubes or tracheostomies are at risk of lower respiratory tract infection because aspiration of contaminated secretions from the oropharynx or stomach is enhanced by several factors, including pooling of secretions above the cuff with subsequent leak and prolonged supine positioning (**Cardenosa Cendrero et al., 1999**).

Any abnormality in the host immune system may predispose a child to develop pneumonia. In particular, viral infections (especially cytomegalovirus) and fungal infections (including Candida and Aspergillus) must be considered (**Gentile et at., 1993**) along with unusual organisms such as Pneumocystis jiroveci (formerly known as Pneunmocystis carinii) or Cryptococcus neoformans.

Malnourished children have an impaired immunologic response (**Chandra, 1991**) and consequently more severe infections. Protein-energy malnutrition may affect

nonspecific and antigen-specific defense mechanisms. The cell-mediated immunologic response is particularly affected changes include atrophy of the thymus and other lymphoid tissues, T Lymphocyte reduction, depressed lymphocyte activation, and impaired delayed hypersensitivity reaction. The humeral response does not seem to be markedly affected, although secretory immunoglobulin A concentrations in several organs, including the respiratory tract, are decreased. Other component of the immunologic system may also be affected by protein-energy malnutrition, including the complement system and phagocytes.

CLASSIFICATION OF PNEUMONIA:

Early classification of pneumonia focused on the anatomic or pathologic appearance of the lung or on the infectious agents , now the most commonly used classification scheme is the combined clinical classification. The advantage of this classification scheme over previous system is that it can help guide the selection of appropriate initial treatments even before the microbiologic cause of the pneumonia is known. There are two broad categories of pneumonia in this scheme: Community-acquired pneumonia and hospital-acquired pneumonia.

(Table 2): Classification of pneumonia by infectious agent:

Classification	Features
Bacterial pneumonia	Common in all ages
Atypical Pneumonia	Due to Mycoplama, Chlamydia, Rickettsiae The older child and young adult are most commonly affected
Viral Pneumpnia	May likely to be serious in patients with weakend resistance

(Golledge, 1997)

(Table 3): Classification of pneumonia by site of infection:

Classification	Features
Lobar pneumonia	More common in bacterial pneumonia
Bronchopneumonia	Patchy or widespread
Interstitial pneumonia	Typical of opportunistic infection

(Golledge, 1997)

(Table 4): Classification of Pneumonia according to likely origin and immune status:

Pneumonia group	Likely pathogen
Community acquired	Gram-positive bacteria Mycoplasma, Chlamydia, Coxiella Common viruses(e.g influenza)
Nosocomial, early	As for Community acquired
Nosocmial, late	Gram-negative enterobacteria Staphylococcus aureus Antibiotic resistant bacteria
Immunocompromised	Opportunistic organism

(Albert et al., 2004)

Table (5): Classification of Pneumonia according to the severity as defined by WHO:

Pneumonia (non -severe)	Cough or difficult breathing plus tachypnea.
Severe pneumonia	Cough or difficult breathing plus tachypnea and lower chest wall indrawing.
Very severe pneumonia	Cough or difficult breathing plus tachypnea and lower chest wall indrawing with at least one of the following: -central cyanosis -inability to breastfeed or drink, or vomiting every thing -convulsions, abnormal sleepy or difficult to wake or unconsciousness -head nodding indicating severe respiratory distress -nasal flaring -grunting.

(Enarson P M, 2005)

I- ETIOLOGIC AGENTS:

A large number of micro-organisms can cause pneumonia in children. the cause of pneumonia in a child is often difficult, but the patient‘s age can help narrow the list of likely etiologies.

(Table 6): Causes of Community-Acquired Pneumonia by Age Group

	Common causes	Less common causes
Birth to 20 days	(Bacteria) Escherichia coli Group B streptococci Listeria monocytogenes.	(Bacteria) Anaerobic organisms Group D streptococei Haemophilus influenzae Streptococcus pneumoniae Ureaplasma urealyticum (Viruses) Cytomegalovirus

	Common causes	Less common causes
		Herpes simplex virus
3 weeks to 3 months	(Bacteria) Chlamydia trachomatis S. pneumoniae (Viruses) Adenovirus Influenza virus Parainfluenza virus 1, 2. and 3 Respiratory syncytial virus	(Bacteria) Bordetella pertussis H. influenzac type B and Non-typable Moraxella catarrhalis Ureaplasma urealyticum (Viruses) Cytomegalovirus
4 months to 5 years	(Bacteria) Chlamydia pneumoniae Mycoplasma - pneumoniae S. peneumoniae (Viruses) influenza virus Para influenza virus Rhinovirus Respiratory syncytial virus	(Bacteria) H. influenzae type B M. catarrhalis Mycobacterium - tuberculosis Neisseria meningitis S. aureus.
5 year to adolescent	(Bacteria) C. Pneumoniae M. pneumoniae S. pneumoniae	(Bacteria) H. influenzae Legionella species M. tuberculosis S. aureus (Viruses) Adenovirus Epstein-Barr virus Influenza virus Parainfluenza virus Rhinovirus Respiratory syncytial virus Varicella-zoster virus

(McIntosh, 2002)

The great majority of respiratory infections are of virus origin.However,10%-50% of patients will develop a secondary bacterial infection **(Hayden, 2006).**Although respiratory viral infections are more studied in developed countries and their impact on health care is well understood, there is a gap in information on the burden of respiratory viral infections in developing countries **(Rudan et al., 2005).**

Viruses are responsible for a large percentage of cases of CAP in the pediatric age group, and they are particularly Common in children aged weeks to 4 years **(Mclntosh, 2002).**

In a US study of children aged 2 month to 17 years who were hospitalized for pneumonia, 45% were found to have a viral etiology **(Michelow et al, 2004**). Respiratory Syncytial Virus, parainfluenza virus, adenovirus, and influenza virus are common known cause of lower respiratory tract disease in infants and children **(Williams 2004**).

Respiratory syncytial virus (RSV) has long been recognized as the main viral pathogen of the lower respiratory tract of infants **(Simoes, 1999).** It causes bronchiolitis in infants, but it is also a cause of classical pneumonias in older children **(Drummond et al., 2000).** Despite its important frequent distinguishing RSV from other ALRTIs is difficult because of the similarities in clinical presentation (**Hussey et al., 2000**); RSV has also been associated with recurrent episodes of wheezing in children **(Schwarzc et al., 1997).**

In 2001,a newly identified paramyxovirus, human metapneumovirus (hMPV), was isolated by Van den Hoogen et al in previously virus-negative nasopharyngeal aspirates from children with respiratory tract infections. Since then, hMPV has been identified worldwide (**Heikkinen et al, 2008**).Although hMPV infections have been diagnosed in all age groups,the virus likely has its greatest effect in children **(Van den Hoogen et al., 2004)**.Clinical symptoms of hMPV infection

resemble those caused by RSV and range from mild upper respiratory tract infections (URl) to wheezing and severe lower respiratory tract illneses (LRTI) that require hospitalizaiion (**Williams et al., 2006**).The most frequent diagnoses in hospitalized children are bronchiolitis and pneumonia,but occasionally hMPV may also cause severe illnesses that require treatment at intensive care units **(SchiLdgen et al., 2005).**

In 2004, **Van der Hoek et al** reported the discovery of a novel human corona virus isolated from a 7-month old girl with coryza.conjunctivitis,fever and bronhiolitis **(Jeffrey, 2007).**This, virus called HCoV-NL63 which has worldwide distribution and has been associated with mid URI,although severe LRTI has been observed. HCoV-NL63 may be responsible for 1-10% of respiratory tract infections and has been associated with croup (**Pyrc et al., 2007**).

In 2005,Allander et al reported the discovery of a novel human parvovirus isolated from children with respiratory tract disease. This novel virus was most closely related to the only 2 members of the Genus Bocavirus. A bovine and canine parvovirus (the term boca was derived from the first *2* letters bo and ca- of bovine and canine) and was called human bocavirus (HBoV).Until the discovery of HBoV, parvovirus B 19 was the only known human pathogen in the parvovirus family (**Jeffrey, 2007**). (HBoV) seems to be a worldwide distributed pathogen and has frequenly been associated with respiratory tract infections among infants and young children **(Volz et al., 2007).**A majority of the HBoV-positive children had rhinorrhea,cough and wheezing **(Kesebir et al., 2006).** An active population-based surveillance in rural Thailand revealed that 4.5% of individuals hospitalized with pneumonia were HBoV-positive and of these, 83% were <5 years old **(Fry et al., 2006).**Unlike patients with RSV-infection **(Simon et al., 2006)** , and similar to those with hMPV-associated respiratory tract infection **(Wilkesman et al., 2006),** children older than 6 months seem to be most at risk

(Manning et al., 2006). HBoV-positive patients also presented with symptoms of gastrointestinal disease **(Arnold et al., 2006).** HBoV-DNA has recently been detected in stool samples of patients unrelated to respiratory infection.raising questions about different possible modes of transmission **(Vicente et al., 2007).**

Bacterial pneumonia is an important cause of morbidity and mortality in children **(Langley and Bradely, 2005).** Concurrent bacterial infection has been reported in 30 - 40% of children hospitalised with viral pneumonia **(Madhi et al., 2000**). S.pneumoniae and H.influenzae remain the leading causes *of* childhood bacterial pneumonia in Low and middle income countries **(Cowgill et al., 2006)**. Pneumococcus (streptococcus pneumoniae) is a common cause of invasive bacterial infections in children and a frequent cause of community-aquired pneumonia **(American Academy of pediatrics, 2009**). Children less than two years of age, immunocompromised patients, asplenic patients are at increased risk of pneumococcal infections (**Rivera-Olivero et al., 2007**).

It is important to remember that a significant proportion of cases of pediatric pneumonia represents a mixed infection **(British Thoracic Society standards of care committee, 2002).** Coinfection with two or more microbial agents is more common than previously thought, with a rate of up to 41 percent in hospitalized patients **(Juven et al., 2000).**

Although most cases of pneumonia is caused by micro-organisms, noninfectious causes include aspiration of food or gastric acid, foreign bodies, hydrocarbons and lipoid substances, hypersensitivity reactions, and drug-or radiation induced pneumonitis **(Kliegman et al., 2007).**

II- CLINICAL FEATURES:

The strongest predictors of pneumonia in children, are fever, cyanosis, and more than one of the following signs of

respiratory distress: tachypnea, cough, nasal flaring, retractions, rales, and decreased breath sounds. Pneumonia should be suspected if tachypnea occurs in a patient younger than two years with a temperature higher than 38°C (100,4°F). Tachypnea widely has been shown to be the most sensitive indicator. Measurement of tachypnea requires a full one-minute count while the child is quiet **(Ostapchuk et al., 2004).** The World Health Organization's age-specific criteria for tachypnea are the most widely used: A respiratory rate of more than 50 breaths per minute in infants two to 12 months of age; more than 40 breaths per minute in children one to five years of age; and more than 30 breaths per minute in children older than five years.

Table (7): World Health Organization Age-Specific Criteria for Tachypnea:

Age	Approximate normal respiratory' rates (bteaths/min)	Tachypnea threshold (breaths/min)
2 to 12 months	25 to 40	50
1 to 5 years	20 to 30	40
≥ 5 years	15 to 25	30

Children without fever or symptoms of respiratory distress are unlikely to have pneumonia **(British Thoracic Society Standards of Care Committee, 2002).**High fever in both infants and children has been considered an important sign in the community, both in developed and developing countries **(Campbell et al., 1989).**Clinical signs may include retractions or abnormal auscultatory findings, such as rales or decreased breath sounds, which tend to be more specific as indicators of lower respiratory tract infection **(Esposito et al., 2002).**Wheezing may be seen in children with bacterial pneumonia but is more suggestive of bronchiolitis or viral lower respiratory tract infection **(Sandora and Harper, 2005).** Wheeze occurs in 30% of mycoplasma pneumonias and is more common in older children **(Broughton, 1986).** Because of this, the clinical

diagnosis of mycoplasma pneumonia without radiography can be confused with asthma.

Other less specific indicators that may be seen in children include malaise, emesis, abdominal pain (reflecting referred pain from the diaphragmatic pleura) and chest pain (which is particularly suggestive of bacterial pneumonia as opposed to viral etiologies, especially when pleuritic in nature).Older children and adolescents are more likely to have findings such as rales, dullness in percussion, bronchial breath sounds, tactile fremitus. and a pleural rub **(Gaston, 2002).**

Clinical picture of pneumonia according to the age:

Infants and toddlers (1-24 Months):

- *Pneumonitis syndrome:* Infants (1-3 months) may present with a characteristic syndrome of cough, tachypnea, progressive respiratory distress arid radiologic evidence of bilateral diffuse pulmonary infiltrates with air trapping. Most are afebrile. The most common pathogens included are Chlamydia trachomatis and respiratory viruses (**Jadavji et al., 1997**).

- *Mild and moderate pneumonia:* Respiratory syncytial virus, parainfluenza, influenza and adenovirus account for most lower respiratory tract infections, including pneumonia, in infants and toddlers. Less frequently isolated viruses include rhinovirus, coronavirus and enterovirus. In most cases illness begins as an upper respiratory tract infection and progresses gradually over several days, with increasing cough and respiratory distress**(Jadavji et al.,1997)**

Severe pneumonia*:* Bacterial pneumonia due to S. pneumoniae. Streptococcus pyogenes, Staphylococcus aureus or H.influcnzae type B(Hib) must be considered in severely ill infants and toddlers with one of the following: rapid onset and progression of symptoms, radiographic evidence of lobar or diffuse infiltrates, large pleural effusion or lung abscess **(Korppi *et* al., 1993).**

Preschool children (2-5 years):

The frequency of viral pneumonia is decreased among children in this age group. The predominant bacterial pathogen is S. pneumoniae. Others , include H.influenzae type B(Hib), nontypable H. influcnza(NTHI). group A streptococci and Staph. aureus (**Claesson et al.. 1989**).

School-aged children and adolescents (6-18 years):

In this age group the most common causes of community-acquired pneumonia in otherwise healthy children are M. pneumoniae and S. pneumoniae. Respiratory viruses, primarily influenza A and B, and adenovirus are found in less than 15% of cases **(Jadavji et al., 1997).**

(Table 8): Features of viral lower respiratory infections (LRTl):

Infants and young children.
- Wheeze.
- Fever < 38.5°C.
- Marked recession.
- Hyperinflation.
- Respiratory rate normal or raised.
- Radiograph shows hyperinflation and, in *15%.* patchy collapse.
- Lobar collapse when severe.

(British Thoracic Society, 2002)

(Table 9): Features of Bacterial lower respiratory infections (LRTl):

- Fever > 38.5 °C.
- Respiratory rate > 50 breaths/min.
- Chest recession.
- Wheeze not a sign of primary bacterial LRT1 (other than mycoplasma).
- Other viruses may be concurrent.
- Clinical and radiological signs of consolidation rather than collapse.

(British Thoracic Society, 2002)

(Table 10): Features of Mycoplasma lower respiratory infections (LRTI):

School children.
- Cough, wheeze, pneumonia.
- Interstitial infiltrates, lobar consolidation and hilar adenopathy.

(British Thoracic Society. 2002)

Types of pneumonia according to the causative pathogen:

Pneumococcal pneumonia:

Pneumococcal pneumonia starts with fever and tachypnea. Since alveoli are poorly endowed with cough receptors, cough only occurs when lysis is present and debris is swept into the airways where cough receptors are plentiful. This accords with the many studies which emphasize the history of fever and breathlessness together with signs of tachypnea, indrawing and unwell appearance ("toxemia").This illness should therefore be considered in febrile tachypneic infants **(British Thoracic Society Standards of Care Committee, 2002).**

Staphylococcal pneumonia:

Pneumonia caused by staphylococcal aureus is a serious and rapidly progressive infection. Infants younger than one year are most commonly affected. Staphylococcal pneumonia in infancy is characterized by abdominal distension, high fever, respiratory distress, and toxemia. It often occurs without predisposing factors or after minor skin infections. The organism is necrotizing, producing bronchoalveotar destruction, Pneumatoceles, pyopneumothorax and empyema are frequently encoutered. Rapid progression *of* disease is characteristic. Frequent chest radiographs to monitor progress of the disease are indicated. Presenting symptoms may be typical of paralytic ileus, suggestive *of* an abdominal catastrophe **(Hay et al, 2005).** S. aureus expresses a variety of

virulence factors including Panton-Valentine Leukocidin (PVL) cytotoxin. PVL is expressed by major methicillin-resistant S.aureus (MRSA) clones, which have now spread through the world **(Vandenesch et al..2003).** PVL causes severe necrotizing pneumonia through its direct toxic activity **(Labanderia-Rey et al.,2007).** Necrotizing S.aureus pneumonia has long been recognized, but the association with PVL was made in 2002, and numerous cases have since been recognized worldwide. Contrary to PLV-negative S.aureus pneumonia, PLV-positive S.aureus pneumonia is often preceded by influenza-like symptoms and is mainly characterized by hemoptysis, pleural effusion, rapid onset of acute respiratory distress. and leucopenia.PLV-positive S.aureus pneumonia is associated with a high fatality rate **(Gillet et al., 2007).**

ATYPICAL PNEUMONIA:

Mycoplasma pneumonia:

Mycoplasma pneumoniae is a common cause of acute respiratory tract infections,especially in school aged children, Mycoplasma pneumoniae accounts for 7%-30% of all community acquired pneumonias in 13-15 year-old children **(Kim et al., 2007).**Transmission is by person-to-person contact, and infection spreads slowly, most often within closed populations (e.g., households, schools).Onset is insidious, over several days to a week. The clinical course of pneumonia caused by M. pneumoniae is usually mild and self-limiled. Constitutional symptoms, which usually are present, include: headache exacerbated by a cough, malaise, myalgia, and sore throat. The cough is usually dry, paroxysmal, and worse at night. Fever, arthralgia, headache. cough and crackles in a schoolchild would suggest mycoplasma infection **(Gaston, 2002),**

M. pneumoniae infection may be associated with several extra pulmonary manifestations. Skin manifestations include erythema multiforme, erythema nodosum, maculopapular and vesicular eruptions, and urticaria. Neurologic derangements

include aseptic meningitis, cerebral ataxia. encephalitis, Guillain-Barre syndrome, and transverse myelitis **(Vervloet et al., 2007).**

Chlamydia pneumonia:

No set of symptoms or signs is unique to pulmonary infections with C. pneumoniae, however, several characteristics of the clinical presentation may help distinguish it from other causes **(Grayston et al., 1993).**Chlamydia trachomatis infection should be suspected in infants who are afebrile or nontoxic and have a dry cough.These patients often have a peripheral eosinophilic pleocytosis (**ostapchuk et al., 2004).** Patients with C.pneumoniae infection often present with sore throat, headache, and a cough that can persist for months if treatment is not initiated early **(Wright et al., 1997).**Cough is very common and is often prolonged. The "staccato" cough is not specific, and crackles are described more frequently than wheeze. The only really significant clinical feature is a history of sticky eye in 50% of cases in the neonatal period. Sputum is usually scant or nonexistent, and a low-grade fever is usually present.Chest radiographs tend to show less extensive infiltrates than are seen with other causes of pneumonia, although significant infiltrates have been reported **(Mc Connell et al., 1994).**

Neither clinical features nor laboratory and radiological investigations, can reliably differentiate infections owing to these so called atypical pathogens from children having pneumococcal pneumonia **(Esposito et al., 2001).** A very high white cell count and C-reactive protein (CRP) level are more suggestive of pneumococcal pneumonia, but either may cause a lobar interstitial picture on chest X-ray. Other investigations too, overlap to an extent that make confident differentiation impossible **(Wubbel et al., 1999).**

CLINICAL ASSESSMENT:

A history and clinical examination are the basis for diagnosing of pneumonia and evaluating the severity of illness (table 5, 11).

Table (11): Clinical Assessment of Community-Acquired Pneumonia in Children:

Clinical Clue	Suggested diagnosis or interpretation
History:	
Day care attendance	Viral infection
Exposure to infectious diseases	Viral or Mycoplasma infection , tuberculosis
Hospitalization	Nosocomial infection
Missing immunizauion	Pneumococcal or Haemophilus influenzae infection , pertussis
Antibiotic therapy within previous month	Infection with resistant bacterial strain
Physical examination:	
Elevated temperature	Pneumonia is unlikely without fever and more than one respiratory sign
Respiratory signs: Grunting Nasal flaring Rales Retractions Tachypnea Use of accessory muscles for breathing Wheezing	In patients with respiratory signs and no fever, consider reactive airway disease, aspiration of foreign body, chemical ingestion, or an underlying cardiac or pulmonary disorders

(Bradley, 2002)

III- INVESTIGATIONS:

In most children with CAP, identification of the causative organism is not critical. Only Patients with severe symptoms, those who are hospitalized, and those who have a complicated

clinical course should undergo diagnostic testing to determine the etiology. The cause also should be determined if there appears to be a community outbreak (**Mc Cracken**, **2000).**

Bacterial and viral pneumonias differ in laboratory and clinical features, but there is enough overlap to prevent reliable differentiation (**Juven et :al., 2001).**

LABORATORY STUDIES:

White blood cell count with differential:

The peripheral white blood cell (WBC) count can be useful in differentiating viral from bacterial pneumonia. In viral pneumnnia, The WBC count can be normal or elevated but is usually not higher than 20000/mm3. with a lymphocyte predominance. Bacterial pneumonia (occasionally adenovirus pneumonia) is often associated with an elevated WBC count 15000-40000/mm^3 and a predominance of granulocytes **(Kliegman et al., 2007).**

Acute-phase reactants:

C-reactive protein and the erythrocyte sedimentation rate, are generally elevated. Acute phase reactants do not distinguish between bacterial and viral infection but can be measured as a baseline and may then only be useful if the patient does not improve on treatment as expected. Most of infections and inflammations result in CRP levels above 10 mg/L, and ESR above 10 mm/hr. (**Korppi et al., 1997).**

Sputum Gram stain and Culture:

It is difficult to obtain a good sputum sample from children, who often have a nonproductive cough. Older children and adolescents may be able to produce sputum for Gram stain and culture. Culture of the sputum has had variable use in published studies, with yields ranging from 5% to 34%. To be considered reliable (ie, bronchial in origin as opposed to oropharyngeal), a sputum sample should contain fewer than ten epithelial cells per low-

powered field. Although a sputum Gram stain with a single predominant organism, leukocytes, and few epithelial cells can be helpful, a negative Gram stain result never should exclude pneumonia as a possible diagnosis **(Sandora and Harper. 2005).**

When symptoms persist despite empiric antibiotic therapy, bronchoscopy with bronchoalveolar lavage (BAL) is a diagnostic option. Several studies have shown that culture of BAL fluid in children with pneumonia can be useful in making a microbiologic diagnosis **(Rock, 1995).**

-Blood culture;

Cultures of the blood for bacteria traditionally have been recommended in consensus guidelines for the diagnosis and management of pneumonia, particularly when a bacterial cause is suspected **(Mandell et al., 2003**) .In children with pneumonia, blood culture yields a sensitivity lower than 10 per cent due to the most of them presents no bacteraemia or due to a previous antibiotic therapy. Moreover, blood culture presents an additional drawback: they may take several days in order to give a positive result **(Mayoral et al, 2005).** However, with increasing resistance to antimicrobial agents, patients with disease severe enough to require hospital admission and parenteral antimicrobial therapy, generally should have cultures of blood sent before therapy. Various organisms may be detected, but S. pneumoniae has been the most frequently isolated pathogen **(Sandora and Harper, 2005).**

-Serologic tests:

-Serum: A number of antigen, antibody, and pneumococcal immune complex methods of serological diagnosis have become available. No single test has specificity and sensitivity sufficiently high to be diagnostic on its own **(British Thoracic Society Standards of Care Committee, 2002**). Viral diagnostics; (either culture or antigen detection using direct fluorescent antibodies) are not

necessary in most routine pneumonia cases, but they can be useful in certain circumstances (including cases that involve immunocompromised patients or to help guide infection control precautions) **(Sandora and Harper. 2005).** Rapid antigen tests are available for RSV, parainfluenza 1, 2, and 3, influenza A and B, and adenovirus. These assays, which are performed on specimens collected from the nasopharynx, can help determine the etiology of viral pneumonia. Nasopharyngeal specimens for bacterial culture or antigen assays are less useful, because bacteria commonly colonize on the nasopharynx **(British Thoracic Society Standards of Care Committee, 2002).**

Mycoplasma infection can be identified using serology. Complement fixation tests: a rise in paired titre is regarded as the gold standard for the diagnosis of M. pneumoniae. IgM ELISA has been shown to reach a diagnostic level during the second week of the disease. Cold agglutinins are often used as an acute test but their value is limited. In children aged 5-14 years the positive predictive value for mycoplasma of a rapid cold agglutinin test was 70% **(British Thoracic Society Standards of Care Committee**, **2002).** Chlamydia pneumoniae may be detected rapidly by direct fluorescent antibodies from a nasopharyngeal specimen or diagnosed by serology **(Sandora and Harper, 2005).**

-urine: Pneumococcal urinary antigen testing is generally not recommended as a diagnostic modality in pediatric pneumonia; despite good sensitivity, the specificity of this test is low (because it is frequently positive in individuals with nasopharyngeal colonization, particularly young children) (**Esposilo et al., 2004**).

Serologic tests often provide only a retrospective diagnosis and are more useful in establishing the causative agent during an outbreak than in treating individual children (**Principi and Esposito, 2001**).

Polymerase Chain Reaction (PCR): Molecular methods such as Polymerase Chain Reaction (PCR) are used with increased frequency for the diagnosis of several infectious disease, including pneumococcal pneumonia, due to their high sensitivity, specificity and speed (**Mayoral et al., 2005**).

Skin tests: The decision to perform a skin test with purified protein derivative in patients who present with pneumonia should be based on the presence of risk factors that would increase the likelihood of tuberculosis or when specific radiographic findings suggest mycobacterial disease (such as the presence of mediastinal adenopathy) (**Sandora and Harper, 2005**).

Arterial blood gas: This test is indicated in any patient with significant respiratory distress to determine the degree of respiratory insufficiency.

RADIOLOGY:

Chest x-ray (CXR):

CXR is the primary imaging study used to confirm the diagnosis of pneumonia. The diagnosis of pneumonia frequently is made or confirmed by the presence of consolidation or infiltrates on chest radiography. The presence of respiratory signs (e.g., cough, tachypnea, and rales) increases the likelihood of a positive chest radiograph. Chest radiography is too insensitive to be useful in differentiating between patients with bacterial pneumonia and those whose pneumonia is nonbacterial (**Clements et al., 2000**). Lobar consolidation classically has been associated with pneumococcal infections, and interstitial infiltrates have been associated with viral infections. However, both lobar consolidation and interstitial infiltrates have been identified in all types of infections: viral alone, bacterial alone, and viral-bacterial (**Korppi et al..1993**).

There is no radiological pattern pathognomonic for mycoplasmal pneumonia. Interstitial infiltrates, lobar

consolidation, and hilar adenopathy have all been described. Pleural effusions are rare (**Guckel et at., 1989**).Chest radiographs should not be obtained routinely in children with mild, uncomplicated lower respiratory tract infection (**British Thoracic, Society Standards of Care Committee, 2002**).

Indications for chest radiographs:

- Ambiguous clinical findings.
- Pneumonia that is prolonged and unresponsive to antibiotic therapy.
- The possibility of complications such as pleural effusions.

(Cincinnati Children's Hospital Medical Center Health Policy and Clinical Effectiveness Program, 2004).

CXR may also be considered in children presenting with high fever, leukocytosis and no obvious focus of infections, since approximately 20% of such children may have radiographic evidence of pneumonia (**Bachur et al, 1999**).

Follow up radiographs:

A follow-up CXR should be done:

(i) In children with lobar collapse.

(ii) To document resolution of a round pneumonia (as this may mimic the appearance of a Ghons focus of primary pulmonary tuberculosis).

(iii) In those with ongoing respiratory symptoms.

Contrasted CT scan:

When children exhibit persistent or progressive symptoms despite seemingly adequate therapy, contrast-enhanced chest CT can be useful in detecting suppurative complications, such as empyema or necrosis that may require further intervention(**Donnelly et al, 1998**).On high-resolution CT, ground-glass opacities. airspace consolidation, nodules, and bronchovascular thickening are common(**Reittner et al. 2000)**

(Table 12) : |Investigations in children hospitalized for pneumonia:

Investigation	**Limitations**	**Usefulness**
Pulse oxymetry / Arterial blood gases		- Accurate measurement of hypoxia and guide use of O2
Chest radiograph	- unable to distinguish etiology	- Assess extent of pneumonia - Detect complications
Blood culture	- Positive in less than 20% of cases - Cost	- Identification of type and susceptibility of bacterial pathogens - Epidemiological surveillance.
Lower respiratory tract secretion (induced sputum, ET aspirate BAL) for P. jiroveci stain .	- Cost - May he difficult to perform	- Diagnosis of PCP. targeted antibiotic therapy
Lower respiratory tract secretion (induced sputum, ET aspirate BAL) for M. tuberculosis stain and culture.	- Positive in some cases only - Induced sputum preferable aspirate or BAL. - Infection control to prevent nosocomial transmission needed.	- Microbiological confirmation of TB - Determine sensitivity of isolate targeted therapy. - Obtain sputum for AFB stain from mother or caregiver if symptomatic.
Three gastric lavages for M. tuberculosis stain and culture	- Positive in a minority of suspected cases, - Requires overnight hospitalization. - Recommended when sputum not possible	- Microbiological confirmation of TB - Determine sensitivity of isolate targeted therapy.
Tuberculin skin test	- False-negative reactions in malnutrition, immunosuppressant, overwhelming infection. - Requires careful technique and reading.	- Evidenvce of TB infection
NPA for viral	- Cost	- Identification of viral

Investigation	**Limitations**	**Usefulness**
detection	- Does not exclude bacterial coinfection	pathogen - Cohorting of patients to prevent nosocomial transmission - Epidemiological surveillance
NPA for C. trachomatis	- Cost, limited availability	- Confirmation of C.trachomatis pneumonia in infants when Chlamydia suspected. - Targeted antibiotic therapy of infant and mother.
Aspiration of pleural fluid for WBC, Glucose, Protein, Gram and AFB stains for Culture	May not be possible in loculated effusions	- Identification of pathogen - Targeted antibiotic -May identify need for intercostal drain insertion
Erythrocyte sedimentation rate, C-reactive protein, WBC, neutrophil count , procalcitonin	Do not accurately distinguish between viral and bacterial pneumonia	Combination of tests may provide some evidence of bacterial infection.

[BAL = bronchoalveolar lavage; ET = endotracheal; AFB = acid-fast bacillus; NPA = nasopharyngeal aspirate; WBC = white cell count; TB = tuberculosis; PCP = Pneumocystis carinii pneumonia]. **(Zar et al, 2005)**

IV- COMPLICATIONS :

Several complications may occur especially in infants and young children. Complications are much commoner with bacterial pneumonias .

Table (13): Complications of pneumonia

Treatment failure caused by antibiotic resistance
Pleural effusion and empyema
Septicemia
Metastatic infection: for example, osteomyelitis or septic arthritis

(British Thoracic Society, 2002)

PLEURAL EFFUSIONS AND EMPYEMA:

Pleural effusions and empyema are known complications of bacterial pneumonia. Effusion occur in at least 40% of bacterial pneumonias, with up to 60% of effusions resulting in the formation of empyema in all age groups **(Schultz et al., 2004).** Parapneumonic effusions are common in children who are hospitalized with pneumonia **(Weinstein et al.. 2004).**

A recent study investigated the serum vascular endothelial growth factor (VEGF) level in children with CAP according to its radiologic type and etiology to see if the serum VEGF levels are related to the pathogenesis of severe complicated Pneumonia. Children with lobar pneumonia with or without effusion showed significantly higher levels of serum VEGF than children with bronchopneumonia concluding that, VEGF may be one of the key mediators that lead to lobar pneumonia and parapneumonic effusion (**Choi et al., 2006**). Whereas S. pneumoniae accounts for most cases with parapnemonic effusions, S. aureus and S. pyogenes are associated with particularly high rates of effusion and empyema (**Hardie et al., 1998**) Tuberculosis is also a common cause in geographic areas with a high prevalence of disease and should be considered in the differential diagnosis

of selected patients **(Valdes et al, 1996).** Characteristics that suggest empyema include pH less than 7.1, lactate dehydrogenase more than 1000 IU/mL, and glucose less than 40 mg/dL (**Light et al., 1980**).Pleural fluid cell count has limited predictive value (**Freij et al, 1984**), and a positive microbiologic diagnosis is made from pleural fluid analysis in less than one third of cases (**Nagler et al, 2001**).

Whereas some effusions resolve with treatment of the underlying pneumonia. others require drainage. A complicated parapneumonic effusion is characterized by loculated pleural fuid that may not be drained adequately by tube thoracostomy alone. Treatment options include prolonged antibiotic therapy, repeated needle aspirations, tube thoracostomy (chest drainage), tube thoracostomy plus intrapleural fibrinolytics, video-assisted thorascopic surgery, and open thoracotomy and decortication (**Weinstein et al., 2004**).

LUNG ABSCESS:

The incidence of lung abscess has decreased dramatically with the antibiotic era. Most lung abscess cases in pediatric patients are believed to develop secondary to bacterial pneumonia. Other predisposing factors for development of lung abscess include immunodeficiency or immunosuppressant states caused by viral infections, severe systemic diseases or steroid therapy and conditions leading to repeated aspiration such as seizure disorders, mental retardation or altered consciousness. Other less common causes of lung abscess are cystic fibrosis. alpha-1 antitrypsin deficiency, anesthesia and dental surgery.

Anaerobic microorganisms are the most common etiological agents leading to lung abscess. Among aerobic microorganisms, S. aureus and Gram-negative bacilli are the most common agents. Fungal and protozoal agents may he seen in immunocompromised patients (**Asher and Leversha, 1998**).

High fever, malaise, and weight loss are often present. Chest radiographs usually reveal single or multiple lung cavities. Air fluid levels can be present. Chest CT scan may provide better localization and understanding of the lesions (**Hay et at., 2005**).

The gold standard therapy for lung abscess is administration of parenteral antibiotics with anaerobic and staphylococcal coverage (**Hirshberg et al.. 1999**). Although 85-90% of patients heal without sequela in response to antibiotic therapy. in 10-15% of patients simple drainage or other surgical interventions are mandatory (**Emanuel et al., 1995**).CT assisted percutaneous drainage is safe and often provides diagnostic and therapeutic value in cases that fail to resolve on antibiotic therapy alone (**Hoffer et al., 1999**).

PREVENTION:

General preventive strategies:

General measures include improved nutrition. micronutrient supplementation with vitamin A and zinc, and attention to indoor environments, particularly avoidance of exposure to passive smoke (**Zar et al., 2003**).

Nutrition:

Attention to adequate nutrition and growth monitoring should be encouraged as malnutrition frequently predisposes children to pneumonia. Breastfeeding has been shown to decrease the incidence of pneumonia in young children by up to 32 % **(Wright et al., 1998).** Breast-feeding protects against acute lower respiratory tract infections(ALRIs) because of breast milk's unique anti-infective properties. It provides passive protection against pathogens (antibacterial and antiviral substances including secretory immunoglobulin A, lactoferrin, oligosaccharides, and cells- macrophages, lymphocytes, and neutrophils), stimulants of the infant's

immune system, and the bifidus factor, which inhibits colonization by Gram-negative species (**Hanson et al., 1990**).

Micronutrient supplementation:

Specific micronutrients that may play a role in prevention of pneumonia include the following:

Vitamin A:

Vitamin A supplementation is effective for reducing the severity of respiratory complications of measles but there is no evidence for protection against non-measles pneumonia. Current evidence supports use of vitamin A supplementation for reducing the severity of respiratory complications of measles. However, the association between vitamin A and non-measles pneumonia is unclear (**Zar et al., 2005**).Routine supplementation with vitamin A for prevention of non-measles pneumonia is therefore currently not recommended.

Zinc:

Daily prophylactic elemental zinc, 10 mg to infants and 20mg to older children, may substantially reduce the incidence of pneumonia, particularly in malnourished children (**Bhandari et al., 2002**). A pooled analysis performed by **Bhutta et al, 1999** of randomized controlled trials of zinc supplementation in children in developing countries found that zinc- supplemented children had significant reduction in pneumonia incidence compared with those receiving placebo.

Reduction in passive smoking:

Caregivers and household members should be encouraged to refrain from smoking and advised on smoking cessation programmes (**Zar et al., 2005**).

Specific preventive strategies:

Immunization: Childhood immunizations have helped greatly in the prevention of pneumonia in children. Pneumonia is a known complication of rubeola, varicella, and pertussis. These illnesses and the pneumonias related to them rarely are seen today because of routine childhood immunizations (Mandell. 2000).

-Routine immunizations:

All children should be given routine immunizations including BCG. measles, diphtheria-pertussis-tetanus toxoid (DPT) vaccines.

-Specific vaccines:

Pneumococcal vaccines:

The 7-Valent Pneumococcal conjugate vaccine (PCV7) is recommended for routine administration to all children 23 mouths and younger at 2, 4, 6, and 12 to 15 months. It is given as 0.5 mL intramuscularly **(American Academy of Pediatrics, 2000**). A recent study showed the effectiveness of the simplified PCV7 schedule based on two PCV7 doses at 3 and 5 months of age, and a booster dose at 11-12 months, can be as immunogenic as the traditional four-dose schedule in the prevention of CAP and acute otitis media (AOM) diseases in which Streptococcus pneumoniae plays a major etiological role (**Esposito et al., 2007**).

(Table 14): Children at high risk of invasive pneumococcal infection:

• **High risk** (attack rate of invasive Pneumococcal disease >150/100 000 cases/y)
1. Sickle cell disease(SCD), congenital or acquired asplenia, or splenic dysfunction.
2. Infection with HIV.

•**Presumed high risk** (attack rate not calculated)

l. Congenital immune deficiency: some B- (humoral) or T-lymphocyte deficiencies, complement deficiercies (particularly C1, C2,C3 and C4 deficiencies) , or phagocytic disorders (excluding chronic granulomatous disease).

2. Chronic cardiac disease (particularly cyanotic congenital heart disease and cardiac failure).

3. Chronic pulmonary disease (including asthma treated with high-dose oral corticosteroid therapy).

4. Cerebrospinal fluid leaks.

5. Chronic renal insufficiency, including nephrotic syndrome.

6. Diseases associated with immunosuppressive therapy or radiation therapy (including malignant neoplasms, leukemias, lymphomas. and Hodgkin's disease) and solid organ transplantation.

7. Diabetes mellitus.

• **Moderate risk** (attack rate of invasive pncumococcal disease >20 cases/100000/y)

I. All children 24-35 months old.

2. Children 36-59 months old attending out-of-home care.

3. Children 36-59 months old who are of Native American (American Indian and Alaska Native) or African American descent.

(**American Academy of Pediatrics, 2000**)

(Table 15): Recommendations for pneumococcal immunization with PCV7 or 23PS* vaccine for children at high risk of pneumococcal disease:

Age	Previous Doses	Recommendations
24-59 mo	4 doses of PCV7	1 dose of 23PS vaccine at 24 mo, at least 6-8 wk after last of PCV7
		1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine
24-59 mo	1-3 doses of PCV7	1 dose of PCV7
		1 dose of 23PS vaccine. 6-8 wk after the last dose of PCV7
		1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine
24-59mo	1 dose of 23PS	2 doses of PCV7, 6-8 wk apart, beginning at least 6-8wk after last dose of 23PS vaccine
		1 dose of 23PS vaccine, 3-5y after the first dose of 23P5 vaccine
24-59mo	None	2 dose of PCV7 6-8wk apart
		1 dose of 23PS vaccine , 6-8wk after the last dose of PCV7
		1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine

*23PS. 23-valent pneumococcal polysaccharide

(**American Academy of Pediatrics, 2000**)

Haemophilus influenzae type b (Hib) vaccines:

The evidence base of the efficacy of Hib conjugate vaccine for the prevention of pneumonia in infants comes from the large randomized trial of Gambia. ln Chile, a post-license Hib vaccination study showed 80 % of effectiveness against Hib bacteraemic pneumonia. The impact of the Hib vaccine on pneumonia after the vaccine introduction was also assessed by linking a retrospective evaluation of hospitalization for pneumonia with the previous dataset of the Hib vaccine effectiveness study **(Sgambatti de Andrade et**

al.. 2004). The recommended vaccination schedule for all available Hib-containing vaccines consists of a primary series (consisting of 2 or 3 doses 2 months apart. depending on the formulation) administered beginning at age 2 months and a booster dose at age 12-15 months **(MMWR**, **2007).** Since the licensure of conjugate H. influenzae type b (Hib) vaccines in late 1990, there has been a > 98% elimination of Hib disease in the USA (**Ward and Zangwill, 1998**).

Influenza vaccine:

The American Academy of Pediatrics (AAP) recommends influenza vaccination for all high-risk children six months of age and older (**Committee of Infectious Diseases, 2002**). Children with chronic Pulmonary, cardiovascular or immunosuppressive disease should be vaccinated annually at the start of the influenza season. Children between 6 months and 9 years of age who have not been vaccinated previously require 2 immunizations of a single dose given 1 month apart (children under 3 years should receive half the adult dose on each of the 2 occasions); children who are older than 9 years or those who have been immunized previously require only a single immunization **(Zar et al., 2005).**

INFECTION CONTROL:

Because pneumonia can be caused by a wide variety of agents. several different infection control precautions may be appropriate. The single most important procedure to prevent the spread of infection in the hospital is hand hygiene (performed either with soap and water or a waterless alcohol based hand sanitizer). Staff also should wear masks when entering the room of patients with influenza (despite the fact that droplet transmission precautions usually only require masks within 3 feet), because several reports have suggested a role for airborne transmission (**Bridges et al., 2003**).

(Table 16): Infection control precautions for specific organisms:

Organism	Precautions [(a)]
Respiratory syncytial virus	Contact
Influenza	Droplet plus mask to enter room, single room
Parainfluenza	Contact
Adenovirus	Droplet and contact
Varicella	Airborne (for chickenpox, non-immune individuals should not enter room): precaution room with anteroom or single room with door closed at all times; zoster in an immunocompromised patient requires airborne and contact precautions
Mycoplasma pneumoniae	Droplet
Bordetella pertussis	Droplet (until patient has received 5 days of effective therapy)
Mycobacterium tuberculosis	Airborne; negative-pressure Precaution room with anteroom
Multidrug-resistant bacteria (methicillin – resistant S. aureus, vancomycin-resistant enterocoocci, resistant gram negative rods	Special organism precautions

Contact refers to gown and gloves; droplet refers to mask within 3 feet; airborne refers to N95 respirator tenterroom: special organism precautions refers to gown and gloves and dedicated patient equipment

(**Bridges et al., 2003)**

V- MANAGEMENT:

Careful attention to specific clinical factors and use of adjunct radiographs and laboratory tests should guide physicians in selection of antibiotics and decisions regarding hospitalization (**Lichenstein et al., 2003**).

HOSPITAL ADMISSION CRITERIA:

The WHO Integrated Management of Childhood illness(IMCI) guidelines define 'danger signs' that indicate severe disease requiring referal to hospital **(Gove, 1997)**

(Table17): Indications for hospital admission :

- All children younger than 2 months.
- Children older than 2 months with:
  - Impaired level of consciousness
  - Inability to drink or eat
  - Cyanosis
  - Stridor in calm child
  - Grunting
  - Severe chest-wall indrawing
  - Room air Sa02 ≤ 92% at sea level or < 90% at Higher altitudes
  - Severe malnutrition
  - Family unable to provide appropriate care
  - Failure to respond to ambulatory care or clinical deterioration on treatment

(**Zar et al., 2005**)

GENERAL MANAGEMENT IN HOSPITAL:

Oxygen therapy:

Mortality from pneumonia is frequently due to hypoxaemia. which can be effectively treated with oxygen. The development of low-flow methods using nasal prongs, nasal catheter or nasopharyngeal catheter has enabled

efficient and cost effective options (**Zar and Madhi, 2006**). Hypoxic infants and children may not appear cyanosed. Agitation may be an indication of hypoxia. Oxygen therapy should be used to treat hypoxia. Hypoxemia can only be accurately assessed if a pulse oxymetry is used. Pulse oxymetry should be performed in every child admitted to hospital with pneumonia. Oxygen saturation (SaO2) measurements provide a non—invasive estimate of arterial oxygenation. To obtain a reliable reading, (1) the child should be still and quiet (2) a good pulse signal (plethysmograph) should be obtained; and (3) once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate stable trace is obtained (**British Thoracic Society Standards of Care Committee, 2002**).

1. When pulse oxymetry is available start oxygen therapy when transcutaneous saturation is less than 90 - 92% in room air.
2. When pulse oxymetry is unavailable, oxygen therapy should be used when there is (i) central cyanosis (ii) lower chest in drawing; (iii) grunting; (iv) restlessness; (v) inability to drink or feed; and (vi) respiratory rate > 70 breaths per minute **(Wang et al., 1996).**

Methods of oxygen administration:

- Nasal prongs are recommended for most children. Nasal prongs give a maximum fractional concentration of inspired oxygen (FiO2) of 28-35% except in small infants when higher concentrations may be obtained. This method does not require humidification of oxygen and ensures that the child receives oxygen during feeding. Oxygen flows of (0.5- 1 L/min) are required in children less than 2 months old and (2 – 3 L/min) in children aged 2 months - 5 years.

- Nasal catheters are usually well tolerated and humidification is not required but they can be blocked by mucus. Oxygen via nasal catheters gives a maximum FiO2 of 35 - 40%.

- Nasopharyngeal catheters have the advantage of requiring the lowest flow rate to achieve a given oxygen concentration in the airways. Infants under 2 months can usually be treated with 0.5 L/min and infants up to 1 year with 1 L/min. However, humidification of oxygen is required and the catheter may easily block. Further, potentially lethal complications including gastric distention, airway obstruction, apnea, pneumo-orbitus and pneumocephalus may occur. Continuous skilled nursing is therefore necessary to prevent these complications. Consequently, oxygen administration via nasopharyngeal catheter is not recommended **(O'Brien et al., 2000).**

- Head box oxygen is well tolerated by young infants. Head box oxygen requires no humidification but requires a high flow and a mixing device to ensure that the correct FiO_2 is delivered. This is the least preferred method as there is wastage of oxygen and the delivered FiO_2 is unpredictable.

- Facemask oxygen is designed to deliver 28% - 65% oxygen at a flow rate of (6-10 L/min).

- In severely hypoxic infants who are not ventilated, oxygen should be administered using a polymask whereby FiO2 concentrations of 60 -80 % may be achieved. The flow rate should be regulated to keep the bag of the mask inflated during inspiration and expiration.

Enteral feeds:

Children with pneumonia should be encouraged to feed orally unless they are: (i) too distressed to drink or swallow safely; (ii) having frequent severe coughing episodes that may be associated with vomiting and possible aspiration of gastric contents; or (iii) hypovolemic with associated poor perfusion. Breastfeeding should be continued where appropriate. If children are too distressed to take fluid and feeds orally, continuous enteral feeds via a nasogastric tube may be provided. Ensuring adequate caloric intake is

essential as there is an excessive demand on the energy reserves in children with pneumonia. in whom the work of breathing is increased. Children should not he starved for more than 24 hours (**Zar et al., 2005**). Where nasogastric tube feeds are used, the smallest tube should be passed down the smallest nostril. There is no evidence that nasogastric feeds given continuously are any better tolerated than bolus feeds (no studies were identified); however, in theory, smaller more frequent feeds are less likely to cause stress to the respiratory system (**British Thoracic Society Standards of Care Committee. 2002**).

Intravenous fluids:

Intravenous fluids must be used with great care and only if there is adequate monitoring available. Indications for intravenous fluid in a child with pneumonia include: (i) Shock (ii) Inability to tolerate enteral feed . In children with severe or complicated pneumonia, serum urea and electrolytes should be measured before instituting intravenous fluids as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is common. In these children, intake should be restricted to 40 - 60% of normal requirements. i.e. 50 ml/kg/day of intravenous fluids. If hyponatraemia is a problem, fluids containing half normal or isotonic saline should be used (**Zar et al., 2005**).

Caloric requirements:

Nutrition is of particular concern especially when there are underlying factors such as malnutrition. The intake of calories should be adequate to meet metabolic requirements and growth. A minimum of 50-60 kcal/kg/day is required by children with pneumonia. In the presence of malnutrition, and following several days of poor nutrition, this needs to be increased considerably (**Zar et al., 2005**).

Physiotherapy:

A recent study by (**Maher et al., 2006**) showed a beneficial effect of low intensity laser physiotherapy in management of infants with pneumonia.

Management of fever and pain:

Antipyretics and analgesics:

Temperature should be treated especially when > 39 °C ,There is a known risk of febrile convulsions and there is central nervous system pathology that may be aggravated by high temperature. Pain associated with Pneumonia may be due to pleurisy or due to pathology involving the upper airways. Pain or discomfort should be treated as it may severely compromise respiratory function and adequate clearance of secretions. The most appropriate agent is paracetamol at a dose of 15 mg/kg/dose given 4-6-hourly. If this does not provide adequate analgesia a mixture of paracetamol and codeine (0.5 mg/kg/dose 8-hourly) is very effective. Aspirin is contraindicated in most children because of the association with Reye's syndrome (**Zar et al., 2005**).

Monitoring:

The frequency of monitoring including heart rate, temperature, respiratory rate, oxygen saturation level, respiratory pattern including chest recession and use of accessory muscles is determined by the child's condition. The sicker the child, the more likely that continuous oxygen saturation monitoring will he needed. Patients on oxygen therapy should have at least 4 hourly observations including oxygen saturation (**British Thoracic Society Standards of Care Committee, 2002**).

Indications for transfer to a Pediatric Intensive Care Unit (PICU):

A very small proportion of children will require ventilatory support for severe CAP. A child should be transferred to an institution where ventilatory support is possible in the following circumstances:

i- Failure to maintain a saturation of > 90% on an FIO2 of > 70% (i.e. on a polymask); or if the partial pressure of arterial oxygen (PaO2):FIO2 ratio is < l00 (normal is 350).

ii- Apnea.

iii- Hypercarbia with resulting acidemia (pH <7.25).

iv- Exhaustion, which may be difficult to judge, but should be considered if a child maintains a high respiratory rate or severe chest-wall indrawing **(Zar et al., 2005)**

Empiric Antibiotic Therapy by Age Group:

One of the major problems in deciding whether to treat a child with CAP with antibiotics is the difficulty in distinguishing bacterial pneumonia (which would benefit from antibiotics) from non-bacterial pneumonia(which would not). As it is difficult to distinguish between pneumonia caused by bacteria and that caused by viral infection, and because of the frequency mixed bacterial-viral infections (at least 30- 40%) children with pneumonia require an antibiotic (**Madhi et al., 2004**).

Treatment decisions are based on the child's age and clinical and epidemiologic factors **(British Thoracic Society Standards of Care Committee, 2002).** The development of pediatric formulations of antibiotics has enabled better therapy in children. Antibiotic therapy should be initiated promptly in children who are thought to have bacterial CAP. Because definitive information about the causative organism is usually unknown, the choice of antibiotic is empiric **(McCracken, 2000**). Pencillin or ampicillin /amoxicillin remain the cornerstone of effective and rational antibiotic

treatment of community-acquired pneumonia in children. A prospective study in the UK ,found an 81% response rate to penicillin in community acquired pneumonia **(Clements et al., 2000**). Amoxycillin is a good drug for outpatient treatment of children below five years with non-severe pneumonia. Even moderately resistant pneumococci will respond to it if the serum and tissue levels are high enough. Since amoxycillin can safely be given at a higher dose, it is a good first choice for pneumonia in children not sick enough to be hospitalized. It is normally given at 40-50 mg/kg a day, but in areas where resistance is common, higher doses of 80-100 mg/kg a day are more effective (**Schrag et al., 2001**).This is because resistance among pneumococci is the result of alterations in the penicillin binding proteins which reduces their affinity for penicillin. Higher drug concentrations are needed for killing the bacteria **(British Thoracic Society. 2001).**.

A multicenter study reported that parenteral pencillin G had similar efficacy to oral amoxicillin for treatment of severe pneumonia (**Addo-Yobo et al., 2004**). There is an increase in the incidence of S. pneumoniae in vitro resistance to the beta-lactam antibiotics, as well as other classes of" antibiotics (**Craig, 1998**).Despite increasing in vitro resistance to beta-lactam antibiotics, favorable pharmacodynamic and pharmacokinetic properties of these antibiotics still make them the treatment of choice when managing pneumonia, even when due pneumococcal isolates with low or intermediate resistance to the beta—lactam antibiotics (**Addo-Yobo et al., 2004**).

Mycoplasma, Chlamydia and other "atypical" pathogens can cause severe pneumonia and death **(Lim et al, 2001).** These organisms do not respond to the beta lactams that we have traditionally used to treat pneumonia. The drugs of choice for these intracellular organisms are the macrolides. The older macrolide, erythromycin, is also effective in community acquired pneumonia **(Chien et al., 1993).**

However, it needs to be taken four times a day. and frequent gastrointestinal adverse effects make adherence difficult. Newer macrolides such as azithromycin and clarithromycin have good activity against M. pneumoniae, C. pneumoniae, and Legionella species, and generally are better tolerated than erythromycin (**Vergis et al., 2000**).Azithromycin has good cure rates and a low incidence of side effects (**Harris et al., 1998**), besides the convenience of a single daily dose.

When S. aureus is suspected, This should be considered if there is radiological evidence of pneumatocele, empyema or abscess formation or if the child remains feverish 48 hours after starting amoxicillin (**Madhi et al., 2000**). In all ages, if features that suggest S. aureus are present, oxacillin or vancomycin should be added, depending on the prevalence of methicillin resistant staphylococcus in the community (**McIntosh, 2002**).

A recent study demonstrated that levofloxacin was as well tolerated and effective as standard of care therapy (amoxicillin/clavulanate ceftriaxone, clarithrornycin, erythromycin) for treatment of CAP in infants and children. Levofloxacin administered 10mg/kg/day as a single dose in children ≥5years and 20mg/kg/day in 2 divided doses in children < 5 years (up to 500 mg/day) for 10 days was well tolerated **(Bradey et al., 2007).**

Management Decisions according to the patient's age:

INFANTS:

Infants three weeks to three months of age who are suspected of having bacterial pneumonia require immediate attention, particularly if they are febrile, tachypneic, or appear toxic **(Gaston, 2002)** These patients are best treated in a hospital; Initial therapy consists of cefuroxime or cefotaxime (**Alberta Clinical Practice Guidelines Steering Committee, 2002**). Blood, urine, and cerebrospinal fluid cultures; a complete blood count with differential and a chest

radiograph should be obtained (**McIntosh, 2002**).Once stabilized, infants may be changed to an oral antibiotic for 10 days.

If C. trachomatis infection is suspected, treatment guidelines recommend outpatient treatment with an oral macrolide and close follow-up (**Gaston, 2002**).

PRESCHOOL-AGED CHILDREN:

Viruses cause most cases of pneumonia in preschool-aged children (i.e.. four months to five years of age). Although most physicians start antibiotic therapy, guidelines allow for withholding treatment if a viral etiology is suspected and close follow-up can be ensured (**Bradley. 2002**).

These children usually have associated symptoms of viral infection, such as pharyngitis, rhinorrhea, and diarrhea (**British Thoracic Society Standards of Care committee. 2002**).

Pneumococcal infection is the most common cause of bacterial pneumonia in this age group (**Peter, 1999**).A child suspected of having pneumococcal pneumonia who is not hypoxic, in distress, or unstable can be treated empirically with high-dosage amoxicillin. The physician may also initiate therapy with a single dose of ceftriaxone (**Cincinnati Children's Hospital Medical Center Health Policy and Clinical Effectiveness Program, 2004**).

Alternatives include amoxicillin-clavulanic acid, azithromycin, cefaclor, clarithromycin, and erythromycin. Preschool-aged children who require hospital admission are treated with cefuroxime or cefotaxime (**Alberta Clinical Practice Guidelines Steering Committee, 2002**). Once the child is afebrile and stable, he or she is switched to an oral antibiotic and treated on an outpatient basis.

Older children:

S. pneumoniae is a significant pathogen in school-aged children and adolescents (i.e., five to 18 years of age) with CAP. Mycoplasma pneumoniae infection also is more common in these children than in other age groups **(British Thoracic Society Standards of Care Committee, 2002).**lf M. pneumoniae infection is suspected, a macrolide antibiotic is the drug of choice (**Nelson, 2000**). Azithrornycin, erythromycin, or clarithromycin may be used as a single agent in this age group because all of these agents provide adequate coverage for penicillin- sensitive pneumococci **(Gaston, 2002).**Therapeutic options for hospitalized patients are cefuroxime or cefotaxime in addition to a macrolide (**Alberta Clinical Practice Guidelines Steering Committee, 2002**).

Antibiotic Therapy for Specific Pathogens:

Antibiotic decisions must be driven by the likely organism. bearing in mind the age of the patient, the history of exposure, the possibility of resistance (which may vary, depending on local resistance patterns). and other pertinent history. Once a specific pathogen has been identified, coverage can be narrowed accordingly.

Most cases can be managed with oral antibiotics. Parenteral therapy is needed only for children with severe pneumonia, disturbed consciousness, improper swallowing, frequent vomiting, and suspected drug malabsorption. Amoxycillin is a good parenteral drug for children with mild pneumonia, but children with severe pneumonia and life threatening disease should be given either a broad spectrum cephalosporin, or the amoxicillin-clavulanate combination.

Children with pneumonia severe enough to be hospitalized should receive an intravenous beta-lactam, such as cefuroxime, ceftriaxone sodium, cefotaxime sodium, or a

combination of a beta-lactam and beta lactamase inhibitor, plus a macrolide **(Heffelfinger et al., 2000).** Young infants should receive a beta lactam and an aminoglycoside, because of their tendency to get Gram negative infections.

Children should be switched to oral therapy as soon as they have improved sufficiently. This reduces cost of therapy, allows early discharge from hospital, and reduces the risk of nosocomial infections and complications like phlebitis. When the initial therapy is a broad spectrum parenteral cephalosporin. the change should be to oral amoxycillin—clavulanate rather than an oral cephalosporin (**British Thoracic Society 2001**).

Duration of therapy:

Antibiotic therapy should he continued for 7 to 10 days in patients with uncomplicated CAP, although no controlled study of the optimal treatment duration exists (**Alberta Clinical Practice Guidelines Steering Committee, 2002**).There are data to suggest that a 7- to 14-day course of therapy (or a 5-day course of azithromycin) is adequate for the treatment of C. pneumoniae. (**Mandell et al., 2003**).For pneumococcal pneumonia, treatment probably should continue until the patient has been afebrile for 72 hours, and the total duration of therapy probably should not be less than 10 to 14 days (or 5 days if using azithromycin because of its long tissue half-life).

Some data suggest that shorter courses of therapy may be equivalent to current standards, although more controlled studies are needed before this practice can be recommended routinely (**Dunbar et al., 2003**) follow-up for outpatients should be done at 24 to 72 hours after diagnosis. Re-evaluation is necessary in children who continue to have unresolved symptoms or fever at 48 hours after diagnosis. In these patients, physicians should suspect inappropriate antibiotic therapy or a lung complication, such as an empyema or abscess (**British Thoracic Society Standards of**

Care Committee, 2002). Asymptomatic children with normal physical findings after treatment do not need follow-up chest radiographs **(Gaston, 2002**).Repeat chest radiographs or computed tomographic scans are recommended if the illness is protracted or a complication such as empyema is suspected (**British Thoracic Society. Standards of Care Committee, 2002**).Penicillin-resistant pneumococci are a concern in the treatment of CAP. Evidence indicates that inpatient intravenous therapy with a penicillin or cephalosporin is effective against penicillin-resistant pneumococci. Oral β-lactam antibiotics are appropriate first-line therapies for patients with ambulatory CAP (**McIntosh, 2002**).

(Table 18) : Management of Community-Acquired Pneumonia:

Patient age	Outpatient	Inpatient	Critically ill
3 weeks to 3 months	If patient is afebrile: Azithromycin, 10 mg per kg orally on day 1. then 5 mg per kg per day on days 2 through 5 or Erythromycin. 30 to 40 mg per kg per day orally in divided doses every 6 hours for 10 days. Admit if patient is febrile or hypoxic.	Erythromycin, 40 mg per kg per day IV in divided doses every 6 hours* If patient is febrile. add one of these agents: Cefotaxime, 200 mg per kg per day IV in divided doses every 8 hours*or Cefuroxime, 150 mg per kg per day IV in divided doses every 8 hours*	Cefotaxime, 200 mg per kg per day IV in divided doses every 8 hours plus cloxacillin, 150 to 200mg per kg per day IV in divided doses every 6 hours. or cefuroxime alone, 150mg per kg per day IV in divided doses every 8 hours*
4 months to 5 years	Amoxicillin. 90 mg per kg per day orally in divided doses every 8 hours for 7 to 10 days. Consider initial dose of ceftriaxone,50mg per kg per day 1M, up to I g per day. Follow with oral therapy for full course. Alternatives: amoxicillin clavulanic acid, azithromyein, cefaclor, clarithromycin, erythromycin	Cefotaxime,150 mg per kg per day IV in divided doses every 6 hours* or Cefuroxime, 150 mg per kg per day IV in divided doses every 8 hours* If the patient has pneumococcal infection: Ampicillin alone. 200 mg per kg per day IV in divided doses every 8 hours*	Cefotaxime, 150 mg per kg per day IV in divided doses every 8 hours plus erythromycin 40mg per kg per day IV or orally in divided doses every 6 hours for 10 to 14 days. or Cefotaxime, 200 mg per kg per day IV in divided doses every 8 hours plus cloxacillin 150 to 200mg per kg per day IV in divided doses every 6 hours for 10 to 14 days.

Patient age	**Outpatient**	**Inpatient**	**Critically ill**
5 years and older	Azithromycin, 10mg per kg (maximum of 500 mg) orally on day1 followed by 5mg per kg Per day on day 2 through 5 or Clarithromcin, 15mg per kg per day orally in divided doses every 12 hours for 7 to 10 days or Erythomycin, 40mg per kg per day orally in divided doses every 6 hours for 7 to 10 days. If the patient has pneumococcal infection: Amoxicillin alone, 90mg per kg per day orally in divided doses every 8 hours.	Cefuroxime, 150mg per kg per day IV in plus. Erythromycin, 40 mg per kg per day IV or orally in divided doses every 6 hours for 10 to 14 days. If pneumococcal infection is confirmed: Ampicillin alone. 200 mg per kg per day IV in divided doses every 8 hours.	Cefuroxime 150 mg per kg per day IV in divided doses every 8 hours plus Erythromycin, 40mgper kg per day IV or orally in divided doses every 6 hours for 10 to 14 days.

(IV – intervenous: IM = intramuscular). duration is total length of IV and oral therapy. Consider switching to oral therapy when child has no complications and is afebrile, clinically improving, not experiencing diarrhea, and tolerating oral intake.

(Cincinnati Children's Hospital Medical Center Health Policy and Clinical Effectiveness Program,2004)

DISCHARGE CRITERIA:

No single set of criteria defining clinical stability for inpatients with pneumonia has gained widespread acceptance, which introduces variability in decisions about discharge.

The combination of normalization of vital Signs, ability to take oral nutrition, and clear mental status has been shown to predict a low risk of subsequent clinical deterioration among hospitalized patients with pneumonia (**Helms and Henderson, 1998**).

OUTPATIENT ANTIMICROBIAL THERAPY:

As medical care for complex patients increasingly shifts from the inpatient to the outpatient arena, a greater number of infections are being treated by continuing the delivery of parenteral antibiotic therapy in the home or at step-down facilities (**Nathwani, 2001**).

Out patient parenteral antimicrobial therapy (OPAT) is a reasonable option for patients with pneumonia who have stabilized clinically in the hospital but are judged to require prolonged parenteral treatment. The treatment of lower respiratory tract infections using OPAT has resulted in excellent clinical outcomes and high levels of patient and physician satisfaction (**Esposito,2001**).

Eligibility for OPAT requires suitable home environment and the selection of an antimicrobial agent with appropriate pharmacokinetic parameters and drug stability to allow reasonable dosing schedule at home **(Tice et al., 2004).** An infectious diseases specialist (or physician knowledgeable about the use of antimicrobial agents in (OPAT) and hospital pharmacist should be involved before discharge in planning for the administration of OPAT. The involvement of discharge planning services in the hospital also can facilitate contact with visiting nurse associations. which can arrange to instruct families in the proper techniques for IV infusions in the home. These agencies can make home visits to observe caregivers and answer questions and obtain blood for laboratory monitoring of disease or medication toxicities. The use of these services, in conjunction with careful follow -up by primary care physicians, provides the best continuity of care from the hospital to the outpatient setting and helps to

ensure that patients with pneumonia receive the highest quality of care across the health care spectrum.

A concern that children in developing countries do not always have access to hospitals, so safe community-based treatments are a preferred alternative that would reduce cost and in-hospital hazards.

A team, led by Donald Thea, Boston University of public health, Boston, USA studied 2037 children between the ages of 3 and 59 months, over seven study sites located in Pakistan, to determine whether home treatment is as safe and effective as in-hospital treatment. The trial was split into two groups, children were selected at random to receive oral amoxicillin syrup and were directed to go home. The other trial group group received IV ampicillin for 48 h as an inpatient. A total of four children from the hospitalized group, and one child from the home group died due to treatment failure. None of the deaths were considered to be associated with treatment allocation and no serious adverse events were reported. The author concluded that, home treatment with high dose oral amoxicillin is equivalent to currently recommended hospitalization and parentral ampicillin for treatment of severe pneumonia. Suggesting that WHO recommendations for treatment of severe pneumonia need to be revised. These findings have motivated the WHO to update and revise the current recommendations on the treatment of severe pneumonia in children (**Hazir et al., 2008**).

Vitamin supplementation:

Vitamin A should not be given to children with acute pneumonia unless this is measles associated **(Brown and Roberts, 2004).** For measles, 200 000 IU vitamin A given on 2 days substantially reduced overall and pneumonia-specific mortality (**D'Souza and D'Souza, 2002**).There is no evidence that vitamin A improves outcome in non-measles pneumonia **(Brown and Roberts, 2004).**

Micronutrient supplementation:

In children with acute pneumonia. adjuvant treatment with 20 mg zinc per day until discharge was found to accelerate recovery from severe pneumonia, reducing the duration of hypoxia **(Brooks et al., 2004).** Zinc should therefore be considered for use in children hospitalized with pneumonia, particularly if there is coexisting malnutrition (**Shakur et al.. 2004**).

RECOMMENDED FOLLOW-UP:

Follow-up of children with pneumonia after discharge from the hospital should include involvement from their pediatrician or other primary care provider to ensure that clinical stability continues and that anitibiotic therapy is completed as prescribed, in otherwise healthy children, follow-up radiographic studies are not necessary after a single episode of pneumonia.

Follow-up radiographs should be reserved for children with underlying conditions, recurrent or persistent symptoms, or recurrent episodes of pneumonia. In these cases, a period of at least 2 to 3 weeks is recommended before obtaining a follow-up radiograph (**Donnelly et al., 1997**).

PROGNOSIS:

For the immunocompetent host in whom bacterial pneumonia is adequately recognized and treated, the survival rate is high. Although most children with viral pneumonia recover uneventfully, worsening reactive airway disease, abnormal pulmonary function or chest radiographs, persistent respiratory insufficiency, and even death may occur in high risk patients such as those with underlying lung, cardiac, or immunodeficiency disease. Patients with adenovirus infection or those concomitantly infected with RSV and second pathogen such is influenza, cytomegalovirus (CMV) or P. jiroveci also have a poorer prognosis (**Hay et al., 2005**).

RECURRENT / PERSISTENT PNEUMONIA:

Recurrent pneumonia has been defined as two episodes of pneumonia in 1 year or three episodes in any time frame. While persistent pneumonia is defined as persistence of symptoms and radiographic abnormalities for more than 1 month (**Wald, 1993**).

For differentiation between recurrent and persistent pneumonia, presence of a symptom free interval during which chest radiographs show clearing of infiltrates, suggests recurrent infection.

Table (19): Etiologic Factors for Recurrent or Persistent Pneumonia:

(A) Congenital Malformations:
1. Airways:
- Cleft Palate
- Pierre Robin syndrome
-Tracheoesophageal fistulae
-Tracheomalacia
2. Lungs: -
-Pulmonary hypoplasia
-Pulmonary sequestration
-Congenital adenomatoid malformation of the lung
-Bronchogenic cysts
3. Cardiovascular:-
-Congenital heart disease, especially left to right shunts and Vascular rings.
(B) Aspirations:
-Gastro-esophageal reflux
-swallowing abnormalities

- Foreign body

-Anomalies of the upper airways

(C) Defects in the clearance of airways secretions:

-Cystic fibrosis

-Abnormalities of the ciliary structure or function

-Abnormal clearance secondary to infections or after repair of congenital defects.

-Airway compression (intrinsic/extrinsic) e.g., mediastinal lylmphadenopath.

(D) Disorders of local / systemic immunity

- Primary immunideficiencies

- Acquired immunodeficiencies (HIV Infection, Immunosuppressive therapy and Malnutrition).

(Lodha and Kabra, 2000)

Aetiologic agents:

There are no systematic data available on the etiologic organinms responsible for recurrent and persistent pneumonia. Tuberculosis is likely to be an important cause of persistent pneumonia. The common organisms responsible for acute LRTI may also be the responsible agents for recurrent infections in a child who is immunocompetent. Infections with cytomegalovirus, Chlamydia may also lead to persistent infiltrates. However, immunocompromised children are more likely to be infected with atypical organisms such as Pneumoystis carinii, fungi, legionella and others (**Stokes, 1999**).

Diagnosis:

A good history and physical examination are mandatory. Based on history and physical examination, the severity of the disorder can be assessed. The following features suggest a severe disorder: (i) Failure to thrive: (ii) Limitation of

activity; (iii) Persistent fever; (iv) Persistent tachypnea and respiratory distress; (v) Persistent hyperinflation; (vi) Significant/sustained hypoxemia; and (vii) Persistent radiographic abnormalities.

Presence of clubbing, growth retardation, increased diameter of the chest indicate chronicity of the disease/infection. It is important to consider each case individually to decide plan of investigations accordingly. It is absolutely necessary to rule out tuberculosis and underlying cardiovascular disease before proceeding to the further investigations.

Radiographic evaluation of chest is essential for localization of infiltrates, their extent and resolution over time in any child having recurrent or persistent pneumonia. Recurrence of infiltrates in same localized area is suggestive of obstruction by a foreign body or congenital anomaly or tumor. Infiltrates which recur in different lobes/segments, are more likely to be seen in generalized disorders such as cystic fibrosis or immunodeficiencies. However recurrence of diffuse infiltrates especially in right middle lobe, lingula or the lower lobes is suggestive of aspiration.

Computed tomography of the chest, magnetic resonance imaging and bronchography may be required for detailed evaluation of the lungs and the airways.

Bronchoscopy is indicated if abnormality of bronchial anatomy or foreign body aspiration is suspected. In addition, bronchoalveohar lavage (BAL) can be performed in at attempt to identify the etiologic agent. The BAL fluid should be subjected to microbiologic evaluation and cytopathology. Isolation of Pseudomonas aeruginosa is a strong pointer to the diagnosis of cystic fibrosis. Demonstration of Pneumocystis carinii suggests underlying immunodeficiency (**Lodha and Kabra, 2000**).

Barium swallow and esophagograms may help in identifying the disorders of swallowing. Radionuclide scans,

esophageal pH monitoring may be done to confirm gastroesophageal reflux. Presence of lipid laden macrophages in bronchial washings has been found to be of value in confirming recurrent or chronic aspiration. Quantitation of lipid laden macrophages in bronchial washing is a better marker of aspiration.

Cystic fibrosis is an important cause of recurrent or persistent pneumonia and is probably underdiagnosed. Sweat chloride estimation should be performed in all children with recurrent or persistent pneumonia.

A systemic immunodeficiency is suspected if in addition to recurrent pneumonias, there is evidence of infection at other sites e.g.. skin, gut, etc. The initial investigations includes complete and differential blood counts, quantitative serum immunoglobulins and skin tests of delayed hypersensitivity. Further investigations may include T and B cell subset quantification. If phagocytic defects are suspected, screening tests include neutrophil count and nitroblue tetrazolium test (NBT) (**Lodha and Kabra, 2000**).

Treatment:

Treatment of recurrent or persistent pneumonia includes therapy for current infection and definitive therapy for underlying disease, which may now always be possible (**Lodha and Kabra, 2000**).

PART II: ZINC

INTRODUCTION:

The health and well being of children depends upon the interaction between their genetic potential and exogenous factors like adequacy of nutrition, safety of environment, social interaction and stimulation **(Singh 2004).** According to caballero (2004), almost two third of the deaths of children around the world are directly or indirectly associated with nutrition defeciencies. Both protien energy-malnuticion and micronutrients defeciencies increase the risk of death from common diseases such as gasroenteritis , pneumonia , and measles **(Caballero ,2004)**

Unicef (1998) defined micronutrients as nutrients that are only needed by the body in minute amounts, which play leading roles in the production of enzymes , hormones and others substances, helping to regulate growth activity, development and functioning of the immune and reproductive system.

Micronutrients of known public health importance include the following : zinc, iron, iodine,copper, vitamins A, E ,C, D, B2, B6 and folate.

Defeciency of these micronutrients can lead to infectious diseaes, blindness, lethargy, reduced learning capacity, mental retardation and in some cases, to death **(Singh, 2004).**

Zinc is one of the essential trace elements; it is the second most abundant trace element in the human body and, as such, a member of one of the major subgroups of the micronutrients that have attained such prominence in human nutrition and health. The human body contains about 2 gm of zinc, approximately 95% of this zinc is found in within cells. About *57%* of the body pool is stored in skeletal muscle, 29%

in bone and 6 %in skin but zinc is found in all body tissues and fluids **(Mason, 2006).**

DIETARY SOURCES OF ZINC:

Zinc is found widely in the food supply, but its bioavailability from different foods is highly variable. Rich sources of zinc include: oysters, red meat, liver and cheese. Zinc in animal products, Crustacean and mollusks is more readily absorbed than from plant foods. Cereal grains, legumes and nuts are rich in phytate (the main storage form of phosphorous in plants), which bind to zinc in the intestine and reduce its absorption. The early cases of zinc deficiency were associated with high phytate-containing foods: unleavened bread from unrefined wheat flour as a dietary staple, and beans (**Samman, 2007**).

The molar ratio of phytate to zinc in the diet has been proposed as a predictor of zinc bioavailability, and ratios greater than 15 have been associated with suboptimal zinc status.

(Table 20): Dietary determinants of zinc bioavailability:

Estimated absorption	Type of diet
Low	• Diet high in unrefined cereal grain • High-phytate soya-protein products as the primary protein source • Phytate : zinc molar ratio > 15 • Calcium > 1 g/day
Moderate	• Mixed diet containing animal or fish protein • Lacto-ovo, ovovegetarion or vegan diets that are not based on unrefined cereals • Phytate : zinc molar ratio < 10 • Bioavailabilily of zinc is improved if the diet includes animal protein sources
High	• Refined diets, low in cereal fibre
	• Phytate : zinc molar ratio < 5
	• Dietary protein primarily from animal food

(Samman, 2007)

ZINC REQUIREMENTS:

The Recommended Dietary Allowance (RDA) is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97-98%) healthy individuals **(Institute of Medicine, 2001).**

(Table 21): Recommended dietary allowance (RDA) by life stage group and gender:-

Life stage group	RDA(mg/day)	
	Male	Female
0 Through 6 months	2[a]	2[a]
7 Through 12 months	3	3
1 Through 3 years	3	3
4 Through 8 years	5	5
9 through 13 years	5	8
14 through 18 years	11	9
19 through 50 years	11	8
>51y	11	8
Pregnancy		
< 18 years	-	12
19 through 51 years	-	11
Lactation		
< 18years	-	13
19 through 51 years	-	12

[a] = Acceptable daily intake. No RDA value was reported

(Institute of Medicine,2001)

Healthy infants are usually able to get an adequate amount of zinc from breastfeeding during the first six months of life, as long as the mother's milk supply is adequate and breast milk is not displaced by complementary foods **(Krebs, 2000),** During the second six months of life when complementary foods are introduced, the risk for zinc deficiency increases because most traditional complementary foods are low in bioavailable zinc **(Krebs and Westcott, 2002).** The prevalence of zinc deficiency throughout childhood is estimated to be high, primarily related to the low consumption of foods high in bioavailable zinc **(Solomons, 2001).**

ZINC METABOLISM :

Absorption can be considered as the processes of influx into the enterocyte and through the basolateral membrane and of transport into the portal circulation. The primary site of absorption of exogenous zinc in the human is thought to be in the proximal small bowel, either the distal duodenum or proximal jejunum **(Krebs et al., 1998).**

Dietary promoters and inhibitors of zinc absorption

Factors known to influence absorption include the amount of zinc present in the intestinal lumen; the presence of dietary promoters (e.g. human milk, animal proteins) or inhibitors (e.g.. phytate, other minerals). Phytate is found in varying amounts in plant products, with grains and legumes having especially high levels.

(Table 22): Compounds facilitating zinc absorption:

Histdine (and other amino acids)	Prostaglandins	Citric acid
d-penicillamine	Metallothionein	Picolinic acid
Essential fatty acids	Glucose	

(Expert group on Vitamins and Minerals. 2002)

(Table 23): Factors associated with decreased zinc absorption:

Dietary	Absence of appropriate absoption ligands	Gastointestinal dysfunction
-Calcium, copper, iron -Phytate (inositol hexaphosphate -Alchol -Fibre -EDTA -Polyunsaturated fatty acids	-Acrodermatitis enteropathica -Hypothyroidism -Cystic fibrosis -Pancreatic dysfunction -Phenylketonuria	-Intestinal mucosal diseas -Malabsorption syndrome -Gastrointestinal surgery

(**Expert group on Vitamins and Minerals, 2002**)

Once absorbed zinc is transported to the liver bound to albumin and, to a lesser extent, a 2-macroglobulin and oligopeptides **(Cousins et al., 1996).** Factors other than zinc intake that influence plasma zinc concentration are hypoalbuminemia, which influences absorption and transport of zinc in infection and other forms of stress, such as organ failure ; tissue injury imposed by surgery and strenuous physical exercise ; pregnancy ; and intestinal disease that interfere with zinc absorption (**Brown, 1998**).

The intestine serves as the major conduit for zinc elimination from body with almost 50% of the daily zinc losses occurring in the gut. However, much of the zinc that is secreted into the intestine is subsequently reabsorbed, and this process serves as an important point of regulation of zinc balance. Other routes of zinc excretion include the urine, which accounts for approximately 15% of total zinc losses, and epithelial cell desquamation, sweat, semen, hair, and menstrual blood, which together account for approximately 17% of total zinc losses **(Food and Nutrition Board & Institute of Medicine (FNB/IOM), 2002**). Starvation and muscle catabolism increase zinc losses in urine. Strenuous exercise and elevated ambient temperatures Could lead to losses by perspiration.

FUNCTIONS OF ZINC:

Zinc is one of the essential trace metals with varied function in humans. Zinc is required for the hepatic synthesis of retinol binding protein, the protein involved in transporting vitamin A. Without adequate zinc,symptoms of vitamin A deficiency can appear even if vitamin A supplements are taken. Zinc also acts as antioxidant, restricting endogenous free radical production act as structural component of the extracellular antioxidant enzyme, superoxide dismutase. It also helps to protect against depletion of vitamin E and maintains tissue concentrations of metallothionein, a possible scavanger of free radicles. Other biochemical processes that

require zinc include carbohydrate metabolism, protein digestion, blood clotting and bone metabolism (**Mason, 2006**).

Zinc is widely recognized as an essential micronutrient with a catalytic role in over a 100 specific metabolic enzymes in human metabolism **(Bhutta and Dewraj, 2004).** As a component of enzymes, known as metalloenzymes, zinc participates in the reaction at the active site or provides structural integrity to the enzyme. Carbonic anhydrase was the first discovered zinc metalloenzyme; other enzymes include: carboxypeptidase. alkaline phosphatase, DNA/RNA polymerase and superoxide dismutase **(King and Cousins, 2006).**

Zinc is one of the most ubiquitous of all trace elements involved in human metabolism and plays multiple roles in the perpetuation of genetic material, including transcription of DNA, translation of RNA, and ultimately cellular division **(International Zinc Nutrition Consultative Group, 2004).** Zinc is important for the structure of Zinc-containing proteints in the human genome, known as "zinc finger proteins', are able to interact with DNA and act as transcriptional mediators **(Samman, 2007).** Zinc-finger family of proteins is one of the most common families of transcription factor in eukaryotic cells and has more than 3,000 members in the human genome. They are known to play a key role in regulating expression of genes important for cell growth, proliferation, differentiation and apoptosis. Owing to their multiple functions, some zinc-finger proteins are powerful regulators in the development of the tumour. However, the role of the remainders at the zinc finger family in tumour development is not clear yet **(Hsieh et al., 2007).**

Zinc plays a role in the structure of biomembranes. A reduction in the concentration of zinc in these membranes results in increased susceptibility to oxidative damage and

alteration in specitic transport systems and receptor sites and these may underlie some of the disorders associated with zinc deficiency. It also plays a role in apoptosis, a critical cellular regulatory proces with implication for growth and development as well as a number of chronic diseases **(Mason, 2006).**

Zinc and Physical Growth:

Zinc deficiency as early as during the intrauterine period may influence the dynamics of physical and intellectual development in humans. In a trial of zinc supplementation during pregnancy, women who received *15m*g of daily zinc, along with iron and folate supplementation, had fetuses with an increased fetal heart rate ranges and more vigorous fetal activity compared to fetuses of nonsupplemented women **(Merialdi et al., 2004).** Although the primary mechanisms whereby zinc influences growth are uncertain, there is a large body of literature indicating that zinc depletion limits growth and development. These include several studies of zinc supplementation among low birth weight infants (LBW) in developing countries indicating significant benefits on weight gain and some benefit on linear growth **(Sur et al., 2003).** Studies from animal models and reports of severe zinc deficiency resulting in dwarfism and delayed sexual maturation in Iranian and Egyptian youth predominantly on a zinc depleted bread diet, suggested that zinc supplementation may have a significant role to play in improved child growth. **(Prasad, 2001).**

A meta-analysis of randomised controlled trials of the effects of supplemental zinc on growth of prepubertal children found that height and weight growth were only moderately improved, and the greatest responses were shown by children who were initially underweight or stunted **(Brown et al., 2002).**

Zinc, Neurodevelopment and Cognition: Zinc may act as a neurotransmitter and by influencing cell division,

maturation, and growth early in fetal life it may determine later neuro development and intellect. Several reviews have examined the relationship between zinc nutrition and children's behaviour and development **(Bhatnagar and Taneja, 2001).**

Trials in Chinese children and Mexican-American children from Texas have found that zinc-supplemented children demonstrated superior neuropsychological performance, particularly in reasoning, when compared with controls. These trials suggest that the beneficial impact of zinc supplementation may have an impact on specific neuropsychological processes that are evident in time-dependent challenging tasks, namely attention and reasoning, rather than in general performance tasks (**Sanstead et al., 1998).**

Although evidence from animal models, psychiatric patients and early studies from infants suggests that zinc deficiency affects cognition, neurodevelopment, responses to stress and emotion, and motor activity, more trials will be needed to evaluate the critical period, risk groups and reversibility of the adverse effects of zinc deficiency on neurodevelopment **(Maureen, 2003).**

Zinc and the immune system:

Zinc is necessary for the normal function of the immune system **(Rink and Gabriel, 2001).** The role of zinc in immune function has been widely documented **(Bhaskaram, 2001).** Several studies indicate a potential role for zinc and supplements that contain zinc in improving immune status **(Fortes et al., 1998).**The immune system is adversely affected by even moderate degrees of zinc deficiency. Severe zinc deficiency depresses immune function (**Shankar and Prasad, 1998**).

The potential benefit of zinc on the immune system can be mediated via a variety of pathways including stabilization of the epithelial barrier, and function of

neutrophils, natural killer cells, monocytes, and macrophages. In addition zinc status may affect lymphocyte counts and function, as well as alterations in the balance of T helper cell and TH1 and TH2 cytokines **(Fraker et al., 2000).**

Influence of zinc depletion on immune functions:

Innate immunity: The innate immunity as the first line of defense represents a natural protection against infections. It is not highly specific and responds to different antigens in the same way. It is not able to produce memory cells. Natural killer (NK) cells are important for immunity against infections and tumors. The natural killer cell number and activity are dependent on the serum zinc level **(Ravaglia et al., 2000).** and it was shown that with zinc deficiency, the NK cell activity and the relative number of precursors of cytolytic cells are decreased **(Prasad, 2000).**

(Table 24): Correlation between zinc concentration and cells of innate immunity:

Cell type	**Zinc deficiency**	**Physiologic normal zinc level**	**High zinc dosage**
Monocytes / macrophages	Decreased functions	Normal	30 μ mol/L: normal >100 μ mol/L: direct activation
Neutrphil granulocytes	Decreased phagocytosis	Normal	100 μ mol/L: normal >500 μ mol/L: direct chemo tactic activity
Natural killer cells	Decreased cytotoxicity	Normal	Suppressed killing

(Klaus-Helge and Lothar. 2003)

Specific immunity: B and T cells of the specific immune system have a great variety of specific receptors (antibodies and T-cell receptors) and can produce memory cells that respond quickly and powerfully to antigens to which they

have been primed. B lymphocytes and their precursors (especially pre-B and immature B cells) are reduced in absolute number during zinc deficiency, whereas changes among mature B lymphocytes are only slight. This might be due to the induction of apoptosis in those cells (**Fraker et al., 2000**).

(Table 25) Correlation between zinc concentration and cells of specific immunity:

Cell type	**Low zinc levels**	**Physiologic zinc level**	**High zinc dosage**
T-cells	Decreased normal functions. increased autoreactivity and alloreactivity	Normal	30 μ mol/L: functions decreased >100 μ mol/L: functions suppressed
B- Cells	Apoptosis	Normal	Apoptosis

(Klaus-Kelge and Lothar ,2003)

T cells : T cells are effector cells as well as important regulating cells of the specific immune system. Zinc influences not only NK cell mediated killing as mentioned above; it also affects the activity of cytolytic T cells (**Minigari et al., 1998**). The relative amount of CD8,CD73, T lymphocytes is found to decrease during zinc deficiency (**Prasad, 2000**). These cells are predominantly precursors of cytotoxic T lymphocytes ($CD8^+$), and CD73 is known to be needed on these cells for antigen recognition and proliferation as well as cytolytic process generation **(Black et al., 1997).** When zinc supplements are given to individuals with low zinc levels, the numbers of *T-cell* lymphocytes circulating in the blood increase and the ability *of* lymphocytes to fight infection improves **(Black, 1998).**

Other Effects of Zinc:

Large doses *of* zinc may reduce copper absorption from the gut and have been used in the treatment of Wilson's disease **(Ferenci, 2004).** Zinc, has been found to be of benefit in the treatment of attention deficit hyperactivity disorder **(Akhondzadeh et al.. 2004).** Zinc lozenges are being used for treatment *of* common colds although the evidence presently at best is inconclusive **(Jackson, 2000).**

ZINC IN DIARRHEAL DISEASES:

Strong evidence exists that zinc supplements improve the prognosis of children being treated for diarrhoeal disease. The use of zinc as an adjunct therapy significantly improves the cost effectiveness of standard management of diarrhea **(Robberstad et al., 2004).** Zinc is said to improve absorption of water and electrolytes by helping in early regeneration of intestinal mucosa, restoration *of* enteric enzymes and enhancing humoral and cellular immunity **(Hambidge, 2000).**

Zinc is effective in prevention of diarrhoea: a recent review **(Cohan et al, 2005)** of nine trials showed significant reductions in diarrhoea incidence, and all showed a reduction of some magnitude **(Black, 2003**). A pooled analysis of randomized, controlled trials of zinc supplementation performed in nine low-income countries in Latin America *and* the Caribbean, South and Southeast Asia, and the Western Pacific, demonstrated that supplemental zinc led to an 18% reduction in the incidence of diarrhea and a *25%* reduction in the prevalence *of* diarrhea **(Bhutta et al., 2000)**

Other studies in Bangladesh of using zinc in the treatment of diarrhea in a community setting have also demonstrated substantial reduction in concomitant use of antibiotics by health-care providers **(Baqui et al., 2002),** thus suggesting that there may be additional benefits to the

use of zinc in the treatment of diarrhea. Zinc was also found to have significant therapeutic effects in persistent diarrhea by decreasing duration of episodes, lowering stool frequency and resulting in a 40% reduction of treatment failures or deaths **(Bhutta et al.,2000).**

ZINC IN RESPIRATORY INFECTIONS:

Because of the fundamental role that zinc plays in cellular metabolism, its effect is substantial in cells with a rapid turnover such as the immune system and is therefore said to modulate host resistance to various infections **(Shankar and Prasad, 1998).**

Case reports and observational studies have shown a correlation between low plasma zinc concentrations in children and a greater susceptibility to infections **(Bahl et al., 1998).**

Patients with pneumonia have been found to have lower blood zinc levels as compared to uninfected children **(Kumar et al., 2004).** Even in well nourished children suffering from acute lower respiratory infection, serum zinc levels have been found to be lower **(Shakur et al., 2004).**

Zinc Investigators Collaborative Group has shown that zinc supplementation is known to decrease incidence of pneumonia in children in developing countries **(Zinc Investigators Collaborative Group, 1999).**

A study from India has found that after 120 days of supplementation with oral zinc in dose of 10 mg daily, zinc supplemented children had 45% reduction in the incidence of acute lower respiratory infections **(Sazawal** et **al., 1998).**

The pooled analysis of trials, conducted in India, Jamaica, Peru and Vietnam indicated an overall 41% reduction in the incidence of pneumonia among zinc-supplemented children **(Bhutta et al., 1999).** Another trial from India by Bhandari et al demonstrated that routine zinc supplementation decreases pneumonia by 26% in children 6 months to 3 years of age (**Bhandari et al., 2002).**Another study from India has demonstrated that recovery rates ; from very ill status and from fever in zinc treated boys were 2.6 times and 3 times those in non-zinc treated children but not in girls (**Mahalanabis et al.. 2004).** In another study in children from Bangladesh less than

2 years of age, zinc supplementation resulted in 30% reduction in duration of severe pneumonia with mean reduction of 25% in hospital stay (**Brooks et al., 2004**).

The use of zinc supplements as a preventive modality has been associated with lower mortality, notably that due to pneumonia (**Brooks et al.. 2005**). However, **Bose et al** (**2006**) reported no benefits of a zinc supplement in the management of pneumonia in young children in Tamilnadu, India. Although they were quite thorough in reviewing factors that may have accounted for their negative result, no apparent explanation was forthcoming. A pharmacologic effect of zinc is plausible, but, it is widely accepted that the beneficial effects of zinc supplements in the prevention and treatment of diarrhea and pneumonia are most likely to be due to the prevention or correction of zinc deficiency. Hence, beneficial effects of zinc supplements in the acute management of pneumonia are not to be expected unless the infant or child is zinc deficient (**Hambidge, 2006**).

Effect of zinc in acute lower respiratory tract infections has been studied not as much as effect of zinc in diarrhea. The study of Bose et al (2006) leaves doubt about the more general benefits to be derived from the routine administration of zinc as an adjuvant therapy for pneumonia in young children in the developing world and indicates the priority of the need for additional studies in representative populations (**Hambidge, 2006).**

ZINC DEFICIENCY:

Micronutrient deficiencies are common in children in developing countries **(Mostert et al.. 2005).** Human nuritioual zinc deficient was originally described in 1961 in young men living in Egypt and coincided with the consumption of diets with very low zinc bioavailability due to high phytic acid content **(Wood, 2000).**The first case of severe zinc deficiency was a 21 year-old man who resembled a 10-year-old boy. He displayed symptom that included growth retardation, hypogonadism and delayed sexual maturation. Other manifestations of zinc deficiency reported subsequently include high rates of infection (e.g. pneumonia) and diarrhoea due to an immune deficiency. diverse forms of skin lesions (e.g. eczema and alopecia), impaired wound healing, loss of taste, and night blindness **(Samman, 2007).**

Zinc has received increasing attention because of the available evidence that its deficiency may have grave consequences in humans **(Hambidge, 2000).**

Estimations of the global prevalence of zinc deficiency, based on the availability *of* zinc in national food supplies and on rates of impaired child growth, indicate that approximately one third of the world's population live in countries that have at high risk of zinc deficiency **(International Zinc Nutrition Consultative Group, 2004).**

The World Health Organisation (WHO) considers zinc deficiency to be a major contributor to the burden of disease in developing countries, especially in those with a high mortality rate **(WHO, 2002).**

The International Zinc Nutrition Consultative Group, (2004) has provided estimates of the risk of zinc deficiency in 176 countries based on data from the Food and Agricultural Organisation's food balance sheets. Bioavailable zinc is calculated and compared with the estimated average

requirement. Based on these estimates, it appears that 25% of the populations of south and south-East Asia and Latin America are at risk of inadequate zinc intake, compared with 10% of the population of Western Europe and North America.

Zinc deficiency most often occurs when zinc intake is inadequate or poorly absorbed, when there are increased losses of zinc from the body, or when the body's requirement for zinc increases (**King and Keen, l999**). Malabsorption syndromes such as coeliac disease or chronic diarrhea and inflammatory bowel conditions such as chron's disease and ulcerative colitis, can lead to increased zinc losses and zinc deficiency in this way **(Mason, 2006).**

A number of conditions predispose to zinc deficiency and are related to: decreased intake; decreased absorption; increased losses in conditions such as diarrhoea and excessive vomiting; and increased requirement associated with growth, pregnancy and lactation (**Samman, 2007**).

The problem of marginal, zinc nutriture and status may be widespread because many studies have reported positive growth response in young children who were administered zinc supplements **(Brown et al., 1998).** Based on serum or plasma levels, around 30-50% of children residing in low income settings have low serum or plasma zinc. Mild to moderate zinc deficiency is common in these countries because of a low dietary intake of zinc rich animal-source foods in which zinc is more bioavaliable, high consumption of cereal grains and legumes, which contain inhibitors of zinc absorption and an overall poor dietary intake **(Sazawal et al., 1998)** . Children in these Countries are also frequently affected by enteric infections, which result in excess fecal losses of zinc **(Fontaine, 2001).**

The central role of zinc in cell division, protein synthesis, and growth makes infants, young children, and pregnant women the most vulnerable population groups because of

their elevated requirements for this essential nutrient. Maternal zinc deficiency before and during pregnancy is associated with intrauterine growth retardation, low birth weight and increased risk of misscariage and stillbirths **(Mason, 2006).**Severe zinc deficiency in pregnant women has also been associated with teratogenecity **(Shah and Sachdev,2001).**

The infant is born with zinc reserves; however, this metal in breast milk occurs at much higher relative concentrations, especially in the first three months. Therefore, risk of deficiency of these elements would be expected only under conditions that would adversely interfere with infants' hepatic storage during fetal development, such as prematurity. As a consequence, low-birth-weight or intra-uterine-growth retardation could limit zinc reserves. In a review by **(Scholl and Reilly, 2000),** conditions of compromised fetal development were, in the majority of studies, responsive to maternal zinc supplementation. Scholl and Reilly concluded that the studies "provided support for the possible relationship between maternal zinc status and compromised fetal development and fetal growth potential".

Zinc is commonly the most deficient nutrient in complementary food mixtures fed to infants during weaning **(WHO, 1998).**Zinc deficiency is especially thought to be associated with an increased susceptibility to infection, and a greater severity of disease when infection occurs **(Walker and Black**. **2004).**

In addition, zinc deficiency may compromise behaviors necessary for cognitive functioning including activity and attention (**Bhatnagar and Taneja**, **2001).**Mild zinc deficiency is associated with impaired growth and poor appetite. Severe zinc deficiency is characterized by mood changes, irritability. and lethargy. The most severe deficiency state occur in patients with Acrodermatitis enteropathica (**Hay et al., 2005**).

Acrodermatitis enteropathica (AE) is an inborn error of zinc metabolism that is inherited as an autosomal recessive (AR) disorder. It is characterized clinically by a triad of dermatitis, diarrhea and alopecia although the complete triad is seen in only 20% of the patients. The characteristic distribution of dermatitis over the face, hands, feet and anogenital region is recognized as a cutaneous marker of zinc deficiency. The cutaneous lesions are psoriasiform, erythematous, scaly and crusted plaques. As the disease progresses, these lesions may become vesicobullous, pustular and erosive. Other features, which occur with varying frequency, include stomatitis, apathy, irritability, growth retardation, failure to thrive and delayed wound healing. Delayed puberty and hypogonadism in developing males are some of the longterm effects of zinc deficiency. The ocular manifestations include photophobia, blepharitis, conjunctivitis and corneal dystrophy. Zinc gluconate or sulfate, is administered orally at a dosage of 1-3 mg/kg/d and clinical response is observed within 5-10 days **(Neldner, 2003**).

ASSESSMENT OF ZINC STATUS:

Biochemical indicators are an objective and quantitative means of assessing the zinc status of a population.A convenient and reliable zinc assessment tool is needed to identify subpopulations who are at a risk of zinc deficiency and as an objective guidepost to determine the need for initiation of zinc supplementation or zinc fortification of the food supply, as well to further our limited understanding of the possible associations between zinc status and the risk of developing various chronic diseases and in predicting favorable health outcomes in patient populations **(Wood, 2000).**

Serum or plasma zinc concentration is the best available biomarker of risk of zinc deficiency in populations **(Hotz et al., 2007).** WHO, UNICEF, and International Zinc Nutrition

Consultative Group (IZiNCG) jointly recommend the use of serum zinc concentration for assessment of population zinc status **(Hotz el al., 2007).**

Serum zinc concentration has some important characteristics that make it a good indicator of zinc status for populations:

i- It reflects dietary zinc intake.

ii- It responds consistently to zinc supplementation.

iii-Reference data are available for most age and sex groups **(International Zinc Nutrition Consultative Group, 2007).**

In general, serum zinc concentration reflects a person's usual zinc intake during the previous few weeks or months. However. Plasma zinc levels are also affected by other factors, such as diurnal rhythm, stress, infection, starvation and plasma protein levels **(Wood, 2000).** For example, infection can lower serum zinc concentration, while muscle break down during weight loss can liberate zinc to the circulation and increase serum zinc concentration **(International Zinc Nutrition Consultative Croup, 2007).** For these reasons. serum zinc. concentration may not be a reliable indicator of an individual's zinc status. Nevertheless, the distribution of serum zinc concentrations among a representative sample of a population can be used to assess the risk of zinc deficiency in that population. In addition, because the serum zinc concentration rises consistently in response to zinc supplementation, this indicator can be used as evidence of successful implementation of a zinc intervention program (**Hess et al., 2007**).

Because serum zinc concentrations vary by age group, sex, time of day of the blood collection and fasting status of the individual, lower limits of normal (i.e., the 2.5th percentile) are presented separately for each of these categories, as shown in (Table 26).

(Table 26) Suggested lower cutoffs for serum zinc concentration (mg/L) by age group, sex, time of day and time since last meal Time of day:

Time of day and fasting status	Suggested lower cutoffs for serum zinc concentration (mg/L)		
	<10 years	≥ 10 years	
	Males and females	Males	Non pregnant females
Morning fasting	Not available	0.70	0.74
Morniong non-fasting	0.65	0.66	0.70
Afternoon, non-fasting	0.57	0.59	0.61

Fasting is defined as no food or beverage consumption for at least 8 hours. **(Hess et al ., 2007)**

Reference values for serum zinc concentration are based on results obtained from a large sample of presumably well nourished American who participated in the Second National Health and Nutrition Examination Survey (NHANES II survey) and were free from infection on the day of the blood sample and not taking any medications that may have affected their results **(Hotz et al.,2003).**

International Zinc Nutrition Consultative Group (IZiNCG) recommends that if more than 20% of the population (or population sub-group) has a serum zinc concentration below the relevant cutoff, the whole population (or sub-group) should be considered to be at risk of zinc deficiency **(international Zinc Nutrition Consultative Group, 2004).**

PREVENTION OF ZINC DEFICIENCY:

Zinc deficiency is one of the ten biggest factors contributing to Burden of disease in developing countries with high mortality **(WHO. 2002).** Thus, ensuring adequate levels of zinc intake should be a key component in efforts to reduce child illness, enhance physical growth and decrease mortality in developing countries. Since the problem was highlighted in the World Health Report (2002), calls have increased for supplementation and food fortification, programmes. (**Prasad, 2003**).

There are several approaches to mitigate zinc deficiency (**Black, 2003).** The most important would be to improve the dietary quality and intake of infants, children and women. Routine zinc supplementation in young children is a difficult task, but supplementation of selected subgroups at highest risk of death like low birth weight or the severely malnourished may be possible. The problem would be to combine zinc with other micronutrients as there may be significant interactions between them resulting in decreased bioavailability of the individual micronutrients. Zinc, iron, vitamin A, and copper all potentially interact and interfere with each other's absorption and metabolism when used as single nutrient supplements (**Donangelo et al.,2002**).

Some researchers have questioned the effect of iron fortification on absorption of other nutrients, including zinc. Fortification of foods with iron does not significantly affect zinc absorption. However, large amounts of iron in supplements (greater than 25 mg) may decrease zinc absorption, as can iron in solutions. Taking iron supplements between meals will help decrease its effect on zinc absorption **(Whittaker, 1998).**

To minimise the risk of zinc deficiency, **Zinc Investigators Collaborative Group, (2007**) has been suggested four main dietary strategies that can be used at

the household level to enhance both the content and bioavailability of zinc (and other micronutricnts) in diet.

i- Increasing the production and consumption of foods with high content and bioavailability of zinc like animal- source foods.

ii- Reducing the phytate content of cereal and legume-based staples to enhance zinc (and iron and calcium) absorption through soaking cereal and legume flours in water can reduce the phytate content of certain cereals, like maize and rice,and most legumes,because their phytate is stored in a relatively water soluble form. Hence, phytate can be removed by simply soaking the flours in excess water and draining it off prior to cooking. This practice can reduce the phytate content of unreined maize flour by about 50% (**perlas and Gibson., 2005**). Also, fermentation induced by microbial phytase enzymes derived from naturally occurring microflora on the surface of cereal grains or from microbial starter cultures (**Gibson et al., 1998**) is another method that can induce phytate hydrolysis and decrease its inhibitory effect on zinc absorption. The extent of phytate reduction through fermentation of cereal-flour slurries varies, but reductions of about 50% can be achieved for some cereals (**Hotz and Gibson., 2001**).

iii-Increasing the intake of foods known to enhance zinc absorption, including even a small amount of animal protein from fish, poultry etc. increases zinc absorption. This enhancing effect has been linked with certain amino acid and cysteine-containing peptides released during the digestion of annual protein,forming soluble ligands with zinc (**Desrosiers and Clydesdale. 1989**).

iv- Promoting exclusive breastfeeding from birth to 6 months of age provides full-term normal birthweight infants with their nutrient needs for zinc , and also protects against gastrointestinal infections that can cause excessive zinc losses. When safe and appropriate complementary feeding, including animal-source foods, should be added together with continued, frequent, on-demand breastfeeding.

The WHO, also proposed the use of zinc supplementation or fortification of complementary foods given to breastfed infants starting at six months of age as a means of meeting their requirement for zinc. It has been argued, however, that the inclusion of meat in complementary feeding in developed and developing countries will meet zinc requirements and alleviate the need for supplementation **(Krebs, 2007).**

In Kenyan children aged 6-14 years, the introduction of a meat-based snack over a two-year intervention resulted in increased growth and higher cognitive scores compared with children who consumed a milk- or fat based snack **(Neumann et al., 2007).**Such strategies will have the advantage of improving not only the dietary content and bioavailability of zinc, but also those of other nutrients, such vitamin B12 and iron.

Zinc supplementation has been demonstrated to be beneficial, resulting in increased growth, improved immunity, and decreased morbidity and mortality **(Brown et al**., **2002). Merialdi et al (1999)** reported enhanced neurobehavioral development in the fetuses of zinc supplemented pregnant women. Reduced risk of neural tube defects has been reported with increased total pre conceptional zinc intake independent of other known confounders such as folate intake and sociodemographic factors **(Velie et al., 1999).** However, the results of zinc supplementation trials during pregnancy did not report any significant benefit in terms of reducing immediate infections morbidity in the neonate, There is some preliminary evidence to suggest that prenatal zinc supplements cause reduction in diarrheal and respiratory morbidity in infants throughout the first year of life even when the supplements are not continued after birth **(Shah and Sachdev, 2001).**

Zinc supplementation of babies with low birth weight in India reduced mortality during infancy by a third

(Sazawal et al., 2001) , Zinc supplements increase the growth and weight gain of stunted or underweight children **(Brown et al., 2002).** Supplementation with zinc or zinc and iron together, has been found to improve vitamin A status among all at high risk for deficiency of the three nutrients **(Muno et al., 2000).** In addition, zinc supplementation of HIV-positive children reduces their risk *of* both diarrhea and pneumonia **(Bobat et al., 2005),** which frequently complicate HIV infections. Therefore, zinc supplementation may reduce fatalities from these diseases.

When zinc is provided as a supplement to children in lower-income countries, it reduces the frequency and severity of diarrhea (**Bhutta, 2000**) pneumonia **(Brooks et al., 2005),** and possibly malaria **(Shankar et al., 2000).** Moreover, studies have shown that children who receive *zinc* supplements have lower death rates **(Baqui et al., 2002).**

The World Health Organization recommends zinc only as a curative intervention, either as part of the mineral mix used in the preparation of foods for the treatment of severe malnutrition, or more recently in the treatment of diarrhea **(WHO, 2004).**