Introduction

Neonatal Pneumonia is an important cause of morbidity and mortality among newborn infants,it remains a difficult diseasetoprospectivelyidentify and treat.Clinicalmanifestationsare often nonspecific,sharingrespiratory andhemodynamicsigns withahost ofnon-inflammatoryprocesses.Radiographicand laboratory findings also have alimited predictive value***(Duke et al.,2005).***

The greatest risk of death from pneumonia in childhood is in the neonatal period***(Duke et al., 2005).***

At least one third of the annual10.8 million deaths in children worldwide occur in the first 28 days of life ***(Black et al.,2003)***.

Theaetiologyandepidemiologyofcongenitaland neonatalpneumoniasdependson theclinicalsettingand population that the baby belongs to (e.g. developed/developing world, tertiary/district hospital or community setting); the stage in the perinatal period;thegestational age of the baby, andthe definition of pneumonia.Diagnosis,treatmentandprevention strategies are therefore also dependent on these factors, and will differ depending on the clinical setting ***(Duke et al.,2005).***

Vitamin D insufficiency is widespread and is associated with increased incidence of respiratory tract infections in preliminary studies***(Laaksi et al., 2007 and Autier et al., 2007).***

Cathelicidin, known as LL37, which is cleaved from its precursor hCAP18 is an endogenous antimicrobial peptide active against abroad spectrum of infectious agents including gram negative and positive bacteria,fungi,mycobacteria,and viruses by acting as a chemoattractant for neutrophils and monocytes and has a defined vitamin D-dependent mechanism***(Adams et al.,2008).*** LL37 is highly expressed at barrier sites including respiratory and colonic epithelium,saliva,and skin thus provides an important first line defense mechanism for the innate immune system to respond to infectious insults ***(Durr et al.,2006).***

Vitamin D is involved in regulation of about 1000 human genes. Recent studies suggest that vitamin D may have other actions outside of its classic functions related to bone and calcium homeostasis. The only human cathelicidin, LL37, enhances microbial killing against a broad range of respiratory pathogenes and has a defined vitamin D-dependent mechanism***(Ehab et al., 2010).***

Aim of the Work

The aim of this work is to study plasma level of Cathelicidin(LL37) in congenital pneumonia and to evaluate its relation to 25(OH)D status, and its diagnostic and prognostic value in these cases.

CongenitalPneumonia

Neonatal pneumonia:

Pneumoniais an inflammatory process that may originate in the lung or be afocal complication of acontiguous or systemic inflammatory process. Abnormalitiesofairwaypatencyaswellasalveolar ventilationand perfusionoccurfrequentlyduetovariousmechanisms.These derangementsoftensignificantlyaltergasexchangeanddependent cellularmetabolismin themanytissues andorgansthatdetermine survivalandcontributetoqualityoflifesuchpathologicproblems,su perimposed on the underlying difficulties associated with the transitior fromintrauterinetoextrauterinelife, posecriticalchallengestothe immature human organism.Recognition,prevention,and treatment of these problems are major factors in the care of high-risk newborn infants***(Duke et al.,2005).***

Epidemiology:

It isestimated that 3.9 million of the 10.8 million deaths in children annually worldwide occur in the first 28 days of life***(Black etal.,2003)***.

More than96%ofallneonataldeaths occur in developing countries, and pneumonia accounts for a substantial proportion of these. Intrauterine and early onset pneumonia was found at autopsy

in10–38% of stillborn and 20–63% of liveborn babies who subsequently died ***(Barnett et al.,2001).***

Deaths occurring in the neonatal period each year account for 41% (3.6 million) of all deaths in children under 5 years. The majority of these deaths occur in low income countries and almost 1 million of these deaths are attributable to infectious causes including neonatal sepsis, meningitis and pneumonia ***(Black et al.,2010).***

Congenital pneumonias:

Congenital pneumonias are usually part of a trans-placental infection, while neonatal pneumonias can evolve from intrauterine or postnatal acquisition. Neonatal pneumonia can be classified as early andlate onset***(Duke et al.,2005).***

Early-onset neonatal pneumonia, in general, is defined as a clinical presentation in the first 48 h up to 1 week of life, while late-onset neonatal pneumonia occurs in the next 3 weeks. Intrauterine pneumonia is a subgroup of early-onset neonatal pneumonia.It presents as a stillbirth, low Apgar scores or severe respiratory distress and is usually associated with maternal chorioamnionitis. Infected amniotic fluid is then aspirated in utero, after prolonged rupture of the chorioamniotic membranes, or during delivery of the affected neonate. Congenital pneumonia occurs in the setting of a maternal systemic infection, which may or may not be symptomatic in the mother. Neonatal autopsy studies have determined that intrauterine and early-onset pneumonia occurs in 10–38% of

stillborns and 20–63% of liveborn babies who subsequently died ***(Barnett et al.,2001).***

Birth weight and age of onset strongly determined the mortality risk from pneumonia***(Duke et al.,2005).***

The epidemiology of postpartum and late-onset neonatalpneumonias in general tends to be associated with nosocomial infections, with introduction of pathogens occurring transplacentally via maternal chorioamniotitis or medical intervention. The true incidence of late-onset pneumonia is difficult to determine in neonates since many series do not report the age of onset. The multi-country World Health Organization (WHO). Young Infants Study provides useful data on community acquired neonatal sepsis, including pneumonia. These data however are skewed towards infants seen in hospital outpatient departments and therefore presentations of intrauterine pneumonia or early-onset pneumonia, which occur mainly in the first 48 h of life, may not be well represented***(WHO, 1999).***

Aetiology and pathogenesis:

The epidemiological features of neonatal pneumonia, in general, with their resultant implications for treatment and prevention are sufficiently similar to those of neonatal bacteraemia and meningitis, and therefore can be used to understand the aetiology of the disease. The aetiology of maternal chorioamnionitis has also been used to understand the aetiology of intrauterine and early-onset pneumonia***(Duke et al.,2005)***.

The pathogens associated with neonatal pneumonia include numerous bacteria, fungi and viruses table 1***(Duke et al.,2005).***

Table (1): Pathogens associated with neonatal pneumonia ***(Duke et al., 2005).***

Bacteria	**Viruses**	***Atypical bacteria***
Escherichia coli *Enterobacter aerogenes* *Group B streptococcus (S,agalactiae)* *Group A streptococcus (s.pyogenes)* *Klebsiella spp* *Pseudomonas aeruginosa* *Streptococcus viridans group* *Staphylococcus aureus* *Proteus spp* *Streptococcus pneumonia* *Enterococcus spp* *Haemophilus influenza* *Staphylococcus epidermidis* *Salmonella spp* *Acinobacter spp* *Neisseria meningitides* *Morganella spp* *Serratia spp*	*Herpes simplex virus* *Respiratory syncytial virus* *Human metapneumvirusParainfluenzae viruses1,2.3* *Human cytomegalovirusInfluenzae A and B virusesHuman adenoviruses* *Human immunodeficiency virus* ***Fungi*** *Candida albicans*	*Chlamydia trachomatis* *Ureaplasma urealyticum and U.pavum* *Listeria monocytogenes* *Treponema pallidum* *Mycobacterium tuberculosis* *Pneumocystis jirovecii*

Bacterial pneumonia from infected amniotic fluid or colonization of the birth canal is linked with maternal chorioamnionitis and fetal asphyxia. It is assumed that asphyxia

leads to fetal gasping and aspiration of infected amniotic fluid. This hypothesis is based on the histological finding of amniotic fluid and/or maternal white blood cells in the affected neonatal lungs***(Duke et al.,2005).***

Studies pertaining to neonatal pneumonia contain blood culture data which will underestimate the proportion of cases that are bacterial***(Duke et al.,2005).***

Chlamydia organisms presumably are transmitted at birth during passage through an infected birth canal, although most infants are asymptomatic during the first 24 hours and develop pneumonia only after the first 2 weeks of life***(Heggei et al.,2001).***

Respiratory viral pathogens such as respiratory syncytial virus, influenza, adenovirus, and others may be transmitted shortly after birth by contact with infected family members or caregivers. However, infection by immediate postnatal transmission of these organisms rarely becomes apparent during the first 24 hours***(Ballard et al.,2009).***

Clinical manifestation:

Neonatal pneumonia is suspected in any newborn infant, with respiratory distress the features of which include any of the following: rapid, noisy or difficult breathing, respiratory rate >60 beats/min, chest retractions, cough and/or grunting.

The clinical risk factors and features of neonatal pneumonia are listed in Table 2***(Mathur et al., 2002)***.

Table (2): Clinical risk factors and features of neonatal pneumonia

1-Predisposing factors a-Maternal fever >38 b-Foul smelling liquor c-Prolonged rupture of membrane >24 hours
2- Clinical picture of sepsis a-Poor feeding b-Lethargy c-Hypothermia or hyperthermia d-poor reflexes e-Abdominal distension
3-Chest X –ray suggestive of pneumonia (nodular or coarse patchy infiltrate,diffuse haziness or granularity.air bronchogram,lobar or segmental consolidation):radiological changes not resolved within 48hours.
4- Positivesepsisscreen(any of the following): a-Bands >20% of leucocytes b- Leucocyte count out of reference range c-Raised C reactive protein d-Raised erythrocyte sedimentation rate.

(Mathur et al., 2002)

The differentiation of neonatal pneumonia from noninfectious respiratory conditions such as hyaline membrane disease **(HMD)**, transient tachypnea of newborn and meconium aspiration is problematical since the clinical radiological appearance can be identical, and pathology and radiology services in some facilities may be rudimentary or unavailable. Gestational age of the neonate and time to onset of clinical signs together assist in the clinical diagnosis of pneumonia. However, **HMD** can

occur close to term and intrauterine infection may result in the premature onset of labour. In addition, gestational age assessment may be inaccurate and dependent on the clinical expertise available, so treatment decisions for respiratory distressof the newborn based on the estimated gestational age are not always practical, may be unsafe and may interfere with the true contribution of pneumonia to mortality in the first week of life***(Duke et al.,2005).***

The incidence of factors predicting neonatal pneumonia varies between clinical studies and with the methodology used to study the disease***(Mathur et al.,2002).***

Clinical risk factors of neonatal pneumonia:

Premature rupture of membrane:

Premature rupture of membranes (PROM) is a condition that occurs in pregnancy when there is rupture of the membranes (rupture of the amniotic sac and chorion) more than an hour before the onset of labor. PROM is prolonged when it occurs more than 18 hours before labor. PROM is preterm (PPROM) when it occurs before 37 weeks gestation ***(Deering et al.,2007*)**.

Risk factors for PROM can be a bacterial infection, smoking, or anatomic defect in the structure of the amniotic sac, uterus, or cervix. In some cases, the rupture can spontaneously heal, but in most cases of PPROM, labor begins within 48 hours. When this occurs, it is necessary that the mother receives

treatment to avoid possible infection in the newborn***(Simhan et al.,2005).***

Maternal risk factors for a premature rupture of membranes include chorioamnionitis or sepsis. Association has been found between emotional states of fear in a population and prelabor rupture of membranes at term Fetal factors include prematurity, infection, cord prolapse, or malpresentation***(Santos et al.,2006).***

If chorioamnionitis is present at the time of PPROM, antibiotic therapy is usually given to avoid sepsis, and delivery is indicated. If chorioamnionitis is not present, prompt antibiotic therapy can significantly delay delivery, giving the fetus crucial additional time to mature.In preterm premature rupture of membranes (PPROM), antibiotic therapy should be given to decrease the risk of sepsis. Ampicillin or erythromycin should be administered for 7 days***(Melis et al.,2007).***

Atypical neonatal pneumonia:

Chlamydia trachomatis:

Chlamydia trachomatis pneumonia can occur at 1-3 months of age, manifestedas a protracted onset of staccato cough, usually without wheezing or fever. Findings on chest X-ray include hyperinflation and diffuse bilateral infiltrates with peripheral blood eosinophilia possibly present. Diagnostic testing is usually performed on a nasopharyngeal specimen Treatmentwith amacrolide antibiotic

(erythromycin,clarithromycin or azithromycin). The estimated risk of *C. trachomatis* pneumonia developing in a neonate with maternal colonization is 7%***(Rosenman et al.,2003).***

The interpretation of***C. trachomatis***-associated neonatal pneumonia is hampered because the 'gold standard' of diagnosis by percutaneouslung aspirate is rarely,if ever, performed. The ability now to perform C. *trachomati*s polymerase chain reaction (PCR) testing on nasopharyngeal or endotracheal aspirates from infants with neonatal pneumonia has increased the sensitivity of detection of this pathogen. It is assumed that C. trachomatis contributes significantly to neonatal pneumonia in countries where untreated sexually transmitted diseases in women are common. Studies from Ethiopa, Papua New Guinea and Kenya have detected *C. trachomatis* by direct immunofluorescent staining of the nasopharyngeal aspirates of neonates with radiologically confirmed pneumonia in 16%, 22% and 46% of cases, respectively***(Were et al.,2002)***

Ureaplasma urealyticum and U. parvum:

Among nonbacterial potential pathogens, ***U urealyticum*** and ***U parvum*** have been frequently recovered from endotracheal aspirates shortly after birth in very low birth weight infants and have been variably associated with various adverse pulmonary outcomes, including bronchopulmonary dysplasia BPD***(Katz et al.,2005).***

Colonization of infants by genital mycoplasmal organisms may occur by ascension of the microorganisms from the lower genital tract of the mother at the time of delivery or by direct invasion of the fetus in utero. Congenital pneumonia, bacteremia, meningitis, and death have occurred in infants with very low birth weight due to Ureaplasma or Mycoplasma infection of the lower respiratory tract. In several large studies, chronic lung disease of prematurity or dysplasia has also been associated with the presence of Ureaplasma organisms in the lower respiratory tract, presumably because of low-grade inflammation in the airways that causes a prolonged need for supplemental oxygen coupledwith barotrauma of mechanical ventilation and oxidant damage due to oxygen administration ***(Waites et al.,2005).***

Treponema pallidum:

Fatal cases of congenital syphilis are usually associated with severe pneumonitis (pneumonia alba) and hypoxaemia, especially in developing countries***(Duke et al.,2002)***.

Respiratory viruses:

The role of respiratory viruses ***(RSV, influenza, parainfluenzaviruses, adenovirus*** and ***metapneumovirus)*** in neonatal pneumonia was described by retrospective reports. These viruses have been associated with seasonal late-onset pneumonia where viral diagnostic techniques are accessible. Nosocomial outbreaks of respiratory viruses in neonatal nurseries and co-infections with ***RSV*** and ***humanmetapneumovirus*****(hMPV)** have been described.Apnea may be the sole presenting feature in neonatal viral pneumonias. The risk of death from neonatal pneumonia is

higher in early-onset disease, hypoxaemia, low birth weight and absence of tachypnea***(Semple et al.,2005).***

Human immunodeficiency virus:

A persistent neonatal pneumonia associated with a rapidly progressive presentation of congenital human immuno-deficiency virus (HIV) infection been described in two southern African studies***(Aiken et al.,2004).***

Infants with congenital HIV infection may present withpersistent pneumonia and rapid progression.Co-infection with tuberculosis,syphilis and cytomegalovirus infection is common in this group of infants***(Pillay et al.,2001).***

Mycobactrium Tuberculosis:

Infants may acquire tuberculosis (TB) by transplacental spread, aspiration or ingestion of infected amniotic fluid, or airborne inoculation fromclosecontacts(family members or nursery personnel).Approximately 50% of children born to mothers with active TB develop the disease during the first year of lifeif chemoprophylaxis or BCG vaccine is not given***(Skevaki et al.,2005).***

Listeria monocytogenes:

Transplacental infection with Listeria monocytogenes can result in fetaldissemination with granuloma formation (skin, liver,adrenals, lymphatics, lungsand brain)calledgranulomatosisinfantisepticum.