PROCALCITONIN AS AN EARLY AND RELIABLE MARKER OF NEONATAL SEPSIS

Dissertation Submitted for

MD DEGREE EXAMINATION
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COIMBATORE MEDICAL COLLEGE & HOSPITAL

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THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

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CERTIFICATE

Certified that this dissertation entitled "**PROCALCITONIN AS AN EARLY AND RELIABLE MARKER OF NEONATAL SEPSIS"** is a bonafide work done by Dr.J.FOUZIYA PARVEEN,M.D post graduate student of pediatric medicine, Coimbatore Medical College & Hospital, Coimbatore 641018 during the academic year 2010-2013.

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DECLARATION

I declare that this dissertation entitled **"PROCALCITONIN AS AN EARLY AND RELIABE MARKER OF NEONATAL SEPSIS"** has been conducted by me at NICU, Department of pediatrics, Coimbatore Medical College and Hospital, under the guidance and supervision of my Chief Prof. Dr. K.NEELAKANDAN, MD, DCH. It is submitted in part of fulfillment of the award of the degree of M.D [Pediatrics] for the APRIL 2013 examination to be held under The Tamil Nadu Dr. M.G.R Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

[DR.J.FOUZIYA PARVEEN]

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25

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TABLE OF CONTENTS

INTRODUCTION

Infection as a prime cause or a complication of other illness is the major cause of mortality and morbidity throughout the world in neonates. Early recognition, diagnosis and treatment of serious infections in the neonates are mandatory because of poor defense; newborn cannot localize the pathogens, which can easily spread to multiple organs. Lack of intervention at an early stage leads to mortality or severe sequelae. Progression from mild symptoms to death occurs more rapidly[1].Most neonatal bacterial infections have an early bacteraemic phase preceding the development of full blown septicemia or localization of infection in organs and tissues. During this phase the clinical signs are subtle, but this is when the treatment must be started if there is to be intact survival.

Neonatal sepsis is classified into early onset sepsis and late onset sepsis.

Early onset sepsis (EOS): It develops within 72hrs of life. Organisms present in genital tract or in labour room and operation theatre are most common causes. Most cases are due to gram negative organisms like E.Coli, Klebsiella and Enterobacter species in our country.

Late onset sepsis (LOS): It develops after 72 hrs of life due to community or hospital acquired infection. Two third of LOS is caused by gram negative organisms such as Klebsiella pneumoniae, Enterobacter,

E.Coli, Pseudomonas aeruginosa, Alcaligenes faecalis, Salmonella typhimurium, Proteus, Citrobacter and Serratia. Rest is caused by gram positive organisms such as Coagulase negative staphylococcus (CONS) and Staph aureus.

WHO clinical criteria for the diagnosis of sepsis in young infant[2]: Convulsion, respiratory rate >60 breaths/min, severe chest indrawing, temperature >37.7 degree Celsius or <35.5 degree Celsius, lethargic or unconscious, reduced movements, not able to feed, crepitations, cyanosis, reduced capillary refill time.

In early stages signs are subtle and non specific. Following are symptoms and signs of neonatal sepsis.

Going off: This is the earliest sign often overlooked. Mother or experienced nurse thinks baby is not right. Baby may be slightly floppy, pale or mottled. The infant may be slightly irritable and poor sucking.

Temperature changes: A temperature below 36 degree Celsius and above 37.8 degree Celsius sustained for more than an hour must be regarded as probably due to infection unless proved otherwise[3, 4]**.**

Gastrointestinal system: Feeding intolerance, abdominal distension due to ileus, vomiting which may contain altered blood and aponea. In

preterm baby apnoea attacks are an early and significant sign of all types of infection.

Respiratory system: Tachypnea - Repiratory rate >60/min, Mild retraction, cyanosis, grunting, dyspnoea.

Cardiovascular system: Tachycardia >160/min[5], Poor cutaneous circulation as evidenced by skin mottling and capillary refilling time > 3 secs.

DIVC (Disseminated intravascular coagulation): In severely ill babies with prolonged hypothermia and acidosis, bleeding manifestations may appear due to consumptive coagulopathy as a result of disseminated intravascular coagulation. There is excessive bleeding from vene puncture site, spontaneous ecchymosis, massive pulmonary hemorrhage and hemorrhagic cerebral infarcts.

Sclerema: In advanced moribund case, the skin assumes hide bound characteristics and is stretched out over the underlying structure. The change begins over skin of the face and legs which becomes unpinchable and subsequently skin changes advance centripetally. When skin of chest is affected, the breathing movements are interfered resulting in shallow rapid breathing and cyanosis[6]**.**

In addition to the above features of disseminated infection, localizing features may appear depending up on the predominant involvement of different systems as discussed below.

Meningitis: About 5 – 15 % of neonates with septicemia may have coexistent meningitis. The evidence of meningeal irritation is generally absent in neonates. Therefore high index of suspicion and frequent resort to lumbar puncture are essential to make an early diagnosis. In a baby with a clinical profile of septicemia, increase in body temperature, onset of seizure or twitching, vacant stare, tense anterior fontanel and irritable cry or excessive cry are signs of meningitis. Meningitis is more common in late onset septicemia .The presence of meningitis prolongs the course of treatment. Late diagnosis and treatment is associated with adverse outcome and increased mortality. Ventriculitis is more commonly associated, when there is congenital anomaly like meningomyelocele and intra ventricular shunt. It is associated with poor clinical or laboratory response to antibiotic therapy. Persistent seizure, bulging anterior fontanel, increasing head circumference and neck stiffness are suggestive of ventriculitis. Sonographic examination would reveal ventricular dilatation, increased echogenicity and septum formation. Ventricular tap shows more than 100 WBCs/cumm. CSF examination with Gram staining may reveal organism. Culture may yield growth.

Pneumonia: May manifest as mild respiratory distress to fulminant hemorrhagic pneumonia with shock. Hence it is advisable to take chest x-ray in babies with neonatal septicemia. Apneic spells with cyanosis, fast breathing and crepitations are suggestive of pulmonary involvement. Cough is a rare manifestation in newborn babies.

Pyelonephritis: The incidence of urinary tract infection in neonates is between 0.1 – 1%. Like sepsis, preterm and male babies are more prone to urinary tract infection (UTI). There are generally no symptomatic clues for the clinical diagnosis of pyelonephritis. Rarely the kidney may be enlarged and palpable. Poor weight gain in spite of adequate feeds may be subtle sign of UTI which mandates urinanalysis and to rule out urinary tract infection.

Osteomyelitis and septic arthritis: Bones and joints involvement are common. Infection may occur through hematogenous spread or from overlying skin directly following venepuncture or overlying skin abscess .The bones and joint infection are most common with Staphylococcus aureus. But it may also caused by other organism. There are classical signs of inflammation like erythema, swelling, tenderness and restriction of movements. Septic arthritis is more common in knee, hip and wrist joints. Osteomyelitis may occur in any bone. Plain skiagram, ultra sonogram, MRI, joint space needle aspiration of pus for gram staining

and culture and sensitivity are diagnostic. Treatment consists of surgical drainage, local immobilization and prolonged antibiotic course of 4 – 6 weeks. Parenteral antibiotic should be advocated at least for 4 weeks. Disability and growth plate damage which will affect bone growth are long term complication.

Necrotising enterocolitis (NEC): It is more common in preterm infants. Perinatal asphyxia is predisposing factor in term pregnancy. There is marked abdominal distension, bile stained vomitus and passage of blood and mucus per rectum. There will be diminished or absent bowel sounds. Abdominal guarding and rigidity may be present due to peritonitis. Severe NEC leads to bowel perforation which can be seen as free air under the diaphragm in x-ray. An inflammatory mass may be palpable in right iliac fossa. Stool examination may reveal occult blood and may be positive for reducing substances. X-ray may show pneumatosis intestinalis or portal gas shadow.

Symptoms and signs pertaining to individual organisms

Gram negative bacilli: In developing countries like India the most common cause of both early onset and late onset sepsis is Gram negative organisms. These consist of diverse group of organisms of widely differing genera. Most of those causing newborn sepsis belong to the Enterobacteriaceae family. The most important organism causing sepsis

in neonates in developing countries are E.coli , Klebsiella pneumoniae, Pseudomonas aeruginosa, Serratia marcescesens, Citrobacter diversus, Proteus mirabilis and Enterobacter cloacae. Sepsis due to gram negative bacilli are usually severe and mortality and morbidity is very high, especially among preterm and low birth weight infants. The presence of grayish-black gangrenous patches on the skin is indicative of septicemia due to Klebsiella and Pseudomonas. The practical utility of this sign is limited because it appears rather late during the course of disease. The baby is often beyond survival when it appears. The mortality rate for pseudomonas sepsis is 23% in India[7]**.** Colonization of airway by gram negative bacilli is usually associated with increased severity of chronic lung disease. Cholestatic liver disease can occur in Gram negative septicemia. Removal of central venous catheters is a mandatory as a part of treatment in most of the cases, particularly when bacteraemia has persisted for more than 24 hours or when there is decreased platelet count.

Coagulase negative staphylococcus (CONS): CONS currently is one of most common cause for late onset sepsis .The CONS is the normal commensal of human skin, where it is found in abundance. They can be identified in the skin of some preterm infants as early as 6 hours of age, and grows rapidly to colonize all infants' skin during the first week of

life. The umbilicus and the nose are the most heavily colonized sites. Infants who are long-stay NICU patients on ventilators and with central venous access are typically infected. Premature infants seem especially vulnerable to CONS sepsis, and their inadequacy of complement mediated opsonic activity against staph. epidermidis may be one of the reason. Sepsis is commonly with slime producing strain[8,9]**.** Slime is a mucinous extracellular polysaccharide substance which helps the adherence of organism to smooth surface such as the silicone or plastic used for intravascular lines, shunts and endotracheal tubes. Slime also prevents neutrophil chemotaxis and phagocytosis and decreases blastogenesis. There are also some reports that the slime also prevents the action of glycopeptide antibiotics such as vancomycin[10]**.**

Most infants present between 7 and 14 days of age. CONS sepsis presentation is widely variable. Rarely the baby is acutely ill and present with all the signs of fulminant sepsis, but more often the presentation in beginning is subtle, even in those with infective endocarditis. Transient apnoeic attacks, fast breathing, skin mottling, abdominal distension, watery stools, occasional vomitus, a few fever spikes up to 37.6 to 38 degree Celsius, the requirement of increased ventilator support are typical. There is significant association between duration of catheter is in place and the risk of infection. Another significant predisposing factor is

the number of times the catheter is used for procedures such as giving drugs or blood transfusions. The infusion of intravenous lipid preparations is an independent predisposing factor to catheter related CONS sepsis.

Blood count changes are fairly common and include a rise in total count and fall in platelet count and hemoglobulin concentration. Fall in level of plasma fibronectin level has a remarkably high specificity of 94% in suspected late onset septicemia among preterm and very low birth weight babies[11].

Staphylococcus aureus: Staph aureus is intrinsically far more pathogenic than CONS. This is partly due to extracellular factors, particularly the α-hemolysin, epidermolytic toxin, enterotoxin, coagulase and leucocidin, and also by surface component such as techoic acid which offers mucosal binding property. Staph aureus remains the commonest cause of infection of skin, umbilical cord and bones and joints, and a common cause of infection of eye. Systemic sepsis carries high morbidity and mortality rates.

Staph aureus access a foothold very easily, and quantitative reports have shown that less than 10 organisms can initiate colonization of the umbilicus. Infection with staph aureus needs earlier action if death or serious morbidity to be prevented. Pustular or impetiginous lesion are

common, which provides a clue to offending organism. Rapid infiltration of organisms occurs especially to bones, joints and lungs. Staph aureus is a relatively remote cause of meningitis and still rarer cause of urinary tract infection. Neonatal Staphylococcal scaled skin syndrome is also reported. Blood and other cultures are generally positive within 24 hours and decrease in neutrophils and platelets are common. The CRP usually rises and values above 100mg/l are often encountered within 12-24 hours of illness.

Group B streptococcus: It is a commensal of GIT and vagina. Most cases of GBS sepsis occur within 4 to 6 hours and almost 90% of cases present within day of birth.GBS sepsis may herald as severe birth asphyxia or occur immediately after resuscitation, with respiratory failure, circulatory failure. Very often the baby presents with early signs of septicemia. Without early recognition and treatment, the baby's condition detoriates rapidly and needs intubation and IPPV for respiratory failure and severe hypoxemia, often showing cardiorespiratory features of persistent pulmonary hypertension of the newborn. Fall in blood pressure, metabolic acidosis, tachycardia and poor perfusion occur in severe cases, then the prognosis is grave.

The hypotension, hypoxia, the liver and lung injury that characterize early onset GBS sepsis in the newborn are very reminiscent of the

systemic inflammatory release syndrome caused by the endotoxins of gram negative organisms. Gram negative endotoxins exert its effect mainly by stimulating the release of cytokines, such as TNF-α, IL -1 and IL -6 from antigen presenting cells, including macrophage and monocytes[12]. TNF-α cause progressive hypotension, decreased cardiac output, hypoxia and lung injury. TNF-α can be detect in serum and urine of babies with GBS sepsis. The cellular component of GBS causing septic shock is thought to be β-hemolysin. Another feature of GBS is its ability to invade pulmonary endothelial cells, especially the cells of microvasculature, and leads to release of the eicasonoids, such as prostacyclin and PGE2, which cause increase in pulmonary arterial pressure and pulmonary and systemic vascular resistance, and decrease in cardiac output and heart rate

A baby is most susceptible to GBS when the mother, despite having GBS in her vagina, has little or no circulating anti GBS IgG. The blood cultures will almost invariably positive if the mother has not been treated with antibiotics. Meningitis is relatively unusual in babies presenting in the first hour of life. But a lumbar puncture should be performed in infants presenting with signs of early onset sepsis. Neutropenia and the presence of primitive cells in the peripheral blood are common. Neutropenia < 1500/l is an ominous sign. Anemia and thrombocytopenia

may develop in survivors. Acute phase reactants such as CRP are generally highly elevated in GBS sepsis, but there may be a delay of 12 hours or so in between onset of signs and rise in CRP. Early acidosis and hypotension are bad signs.

Approximately 1% of newborn born vaginally to the mother who carry GBS at the time of birth become infected. Important predisposing factors are chorioamnionitis, prolonged labour, prolonged rupture of membranes, frequent pelvic examination in labour and low birth weight. When the membranes rupture prior to onset of labour, known simply as premature rupture of membrane (PROM), the interval between membrane rupture and the birth of the baby may be prolonged. When the membrane rupture at less than 37 weeks gestation – known as preterm premature rupture of membrane (PPROM), an even greater interval between membrane rupture and child birth often occurs. The risk of neonatal sepsis following PPROM has been reported to be about 3.5 times that without PPROM[13]**.** Meconium staining of liquor increases risk of intra amniotic infection.

Hemophilus influenza: H.influenzae usually non capsulated strain has an affinity for the female genital tract. Most newborn present immediately after birth with respiratory distress due to pneumonia. Meningitis and conjunctivitis are relatively common. The reported mortality is 50%[14]**.**

Ampicillin resistance is emerging and cofotaxime should be added when there is reason to suspect H.influenzae.

Enterococci: These are mostly non β haemolytic. They are normal bowel organisms which only cause disease when they get out of their proper place. The organisms causing most disease in babies are Entercoccus faecalis and Enterococcus faecium. Enterococci are a notorious cause of nosocomial infection in neonatal intensive care units. In the NICU, Enterococci are an important cause of serious late onset sepsis among VLBW infants.

Listeriosis: L.monocytogenes is a short gram positive rod which can be found both inside and outside cells. The most important reservoir for transmission to humans is probably food, especially dairy products, contaminated by infected farm animals. Woman infected with HIV are more susceptible to L.monocytogenes[15]**.** Newborn infants are particularly susceptible for a variety of immunological reasons, including defect in macrophage response and low opsonic activity.

Three main types of neonatal and fetal infection are found. Transplacental infection, early onset infection acquired intrapartum, late onset infection usually meningitis probably due to nosocomial infection.

Transplacental infection: L.monocytogenes causes non specific influenza or gastroenteritic illness in the pregnant woman, during which the organism may infect the fetus, either by hematogenous spread across the placenta or via infection of the amniotic fluid. First or second trimester infection may cause fetal death or miscarriage, and recurrent abortion. Later in pregnancy, infection may precipitate preterm labour, with fetal distress and meconium staining of liquor. Because meconium staining of liquor is rare at gestation below 34 weeks, its presence should raise the suspicion of Listeria. Live born babies are extremely ill at birth. They may have a severe pneumonia, and hepatomegaly and meningitis may already be present. Blood and stool cultures are invariably positive. Characteristically, small 2-3 mm pink granulomatous lesions are wide spread in the lung, liver, CNS and many other tissue and organs.

Early onset infection acquired intrapartum : Most cases of neonatal listeriosis are sporadic, but epidemics are described. At least two-thirds of infants who acquire listeria infection are preterm, and almost all become ill within 24 hours of life. Most have disseminated infection with pneumonia, meningitis, thrombocytopenia, anaemia and sometimes conjunctivitis. Small cutaneous granuloma may be found in some babies.

Focal bacterial infection

Meningitis: Inflammation, edema and arachnoiditis are widespread in most cases of neonatal meningitis, as are vasculitis and superficial cortical thrombophlebitis, which cause superficial ischemic damage to the brain. Ventriculitis occur in 70-90% of cases of neonatal meningitis, but it is less common with GBS than with gram negative organisms. Severe encephalitic changes often occur, probably as a result of direct penetration of organism in to brain, and may result in wide spread cerebral atrophy. The choroid plexus may be damaged, permanently compromising CSF production, and exudates may obstruct intra ventricular foramina and arachnoid granulations, leading to hydrocephalus in around one third of the cases. Abscess formation is commonly seen with meningitis caused by Citrobacter and Proteus species and occasionally with other Coliforms[16]**.** Abscess formation begins with suppurative ventriculitis and progress to periventricular abscess formation.

Urinary tract infection: Infants of cocaine users seems to be unusually susceptible to UTI[17]**.** UTI in newborn is believed to be occurring mainly as a result of hematogenous spread of organism to the kidney during the septicaemia, although no doubt, the reverse situation can also apply. Breast feeding offers a significant degree of protection.

The commonest pathogen by far is E.coli, and responsible strains are associated with P fimbria, a limited number of serotypes, resistance to bactericidal effect of serum, adhesion to the epithelial cell and production of hemolysin. In addition many gram negative enteric bacteria and gram positive cocci, including CONS, Staph aureus and Enterococci, can cause neonatal UTI. Candida albicans accounts for some 40% of UTI in neonatal unit setting[18]**.** In the case of VLBW babies, this is usually one of the component of multisystem infection.

Investigations

The decision to treat will be mainly determined by clinical assessment. Since septic infants detoriate so rapidly, the threshold for pre-emptive strike with antibiotics should be very low. To improve on this diagnostic accuracy, various tests have been developed and evaluated.

Given the limited predictive power of existing tests, and the fact only few of them can produce results rapidly enough, decisions about antibiotic prescribing for unwell babies should continue to be made on clinical grounds. However, positive test results suggestive of infection may be sufficient reason to begin therapy even when the level of clinical suspicion is not high. The only test results that are more or less immediately available and sufficiently powerful to endorse a decision to go ahead with antibiotic therapy are cerebrospinal fluid (CSF) and urine

microscopy, bacterial antigen test, Buffy coat microscopy and possibly the chest x-ray (CXR). The rest of the tests subserve one or both of the following functions. To provide retrospective evidence for or against the clinical diagnosis of infection. To establish the nature and antimicrobial sensitivity of infecting organisms.

Blood culture: This is the definitive test. Virtually all cultures that are going to be positive have grown by 48 hours whatever the culture method. Possible exceptions are Listeria monocytogenes, H. influenzae and yeasts, which may all take longer time to grow. Blood for culture should be taken before starting or changing antibiotics. Ideally blood for culture should be taken from a peripheral vein after thoroughly cleaning the overlying skin with an antiseptic solution and allowing to dry. Chlorhexidine with alcohol or an iodine containing solution should be used. A better result can be obtained if the skin is cleansed for 30 seconds rather than the usual 5-10 seconds. With good technique, the skin contamination of blood cultures taken from peripheral veins can be reduced to an acceptable level. It is recommended to take 1 ml of blood in a 10-20 ml broth or 0.5 ml blood in 5–10 ml broth[19]**.** Taking two cultures from separate site is a way to reduce false positive diagnosis of infection.

A pure growth appearing with in 24 -48 hours is virtually always significant. Mixed organisms, bizarre organisms and growth that do not

appear until after 72 hours of incubation should raise suspicion. However, in the case of the VLBW infant, it is unwise to ignore bizarre organisms or polymicrobial infection.

CONS present the greatest difficulty, because they colonize the skin of all the babies and yet are the commonest pathogen among NICU inmates. Multiple site blood culture may improve the distinction between genuine septicemia and skin contamination[20].

Hematological investigation

Total white cell count: The total leucocyte count has a low predictive value for the diagnosis of sepsis because of wide range of normal count from 8000 to 20,000/cumm. Leucopenia, less than 5000/cumm is usually associated with neonatal sepsis.

Absolute neutrophil count: The neutrophil count is of more value. Within first 48 hours of life, neutropenia less than $2 – 2.5 \times 10^9$/l suggests bacterial infection, and at this cut off value the sensitivity is around 20%. Thereafter, both neutropenia and neutrophilia have useful predictive power, although in neither case is the specificity or sensitivity greater than about 80%[21].

Normal neutrophil ($\times 10^9$/l) counts in the first month of life:

AGE	MEAN	RANGE
BIRTH	11.1	6 -2 6
12 HOURS	15.5	6 - 28
24 HOURS	11.5	5 - 21
1 WEEK	5.5	1.5 - 10
2 WEEKS	4.5	1 - 9.5
1 MONTH	3.8	1 - 9

Table: 1

Band form: The appearance of circulating neutrophils changes in infection, so that more immature forms are seen in peripheral circulation. These are commonly known as band forms. The absolute value for band forms is not of much use because it tends to rise late in the infection, and in most severely affected infants, band cell production is limited as the marrow becomes exhausted. A slightly more useful indicator of infection is the ratio of immature to total neutrophil (I/T ratio). The maximum normal value is 0.16 during first 24 hours, 0.14 by 48 hours, and 0.13 by 60 hours, where it remains until 5 days of age. Thereafter, the maximum normal I/T ratio is 0.12 until the end of first month. Several studies have found that I/T ratio of > 0.2 is useful marker of neonatal sepsis. An abnormal I/T ratio in the presence of low absolute neutrophil count is more strongly suggestive of sepsis.

Platelet count: In 50 % of babies with bacterial infection, the platelet count will fall below 100×10^9/l, but this usually occurs after the baby is obviously septic. In a recent study, the sensitivity and specificity of thrombocytopenia for the diagnosis of septicemia were reported as 65% and 47% respectively[22].

Micro erythrocyte sedimentation rate: Micro-ESR is a simple, inexpensive but not very reliable marker of neonatal infection. Normal value is up to 6 mm in the first hour during the first 3 day of life. By the end of first month, maximum fall may up to 11 mm. During the neonatal period value more than 15mm is considered as suggestive of infection. Micro-ESR is obtained by collecting capillary blood in a standard pre-heparinized micro- hematocrit tube (75 mm length, internal diameter of 1.1 mm and outer diameter 1.5 mm) and by reading the fall of erythrocyte column after one hour

Acridine orange test: Direct staining of microorganism with in WBCs using the acridine orange technique is a useful way of diagnosing septicemia and fungaemia. Microscopy of a Buffy coat smear stained with methylene blue is also a useful test, with a high rate of concordance with blood culture results.

Lumbar puncture (LP): Neonatal bacterial meningitis carries such a high mortality and morbidity, especially if the diagnosis and treatment are

delayed. A lumbar puncture should be performed as a part of infectious disease work up of most ill babies before antibiotics are started. Exemptions can be made for babies with pulmonary infections complicating long term intermittent positive pressure ventilation, babies with overt localized infection such as NEC or osteomyelitis and babies who would not tolerate the procedure. However there is a slight risk of missing or delaying the diagnosis of meningitis in preterm infants if the LP is omitted from early sepsis screening. In general, the LP is more likely to produce a positive result in late onset than in early onset sepsis[23].

Although high WBC counts in CSF have sometimes been reported in babies without meningitis, a polymorphonuclear count higher than 20/cumm should be regarded with suspicion, and count above 30/cumm are strongly indicative of meningitis. When blood stained CSF is obtained, the ratio of red cells to white cells to be calculated. In uninfected CSF it is usually > 500:1. Gram negative meningitis generally produces a higher CSF white cell count than does GBS meningitis, in which the WBC count is often <100/cumm.

Microscopy of the CSF is crucial and may with caution be used to direct the choice of initial antibiotic therapy, although broad spectrum antibiotic to be used until the results of the culture are known. The isolation of Candida species from the CSF of infants in the absence of other CSF

abnormality usually suggests contamination[24]. If no organisms are seen on Gram stain, latex agglutination testing on the CSF will identify GBS infection with high degree of specificity.

The upper normal limit of CSF protein is 1.5-2 g/l in the term baby. Preterm often have higher CSF protein concentration but rarely greater than 3g/l. The levels are usually raised in meningitis. CSF glucose levels should be related to simultaneous measurement of blood glucose. The CSF glucose should be at least 50% of the blood glucose level. A low level suggests bacterial meningitis.

The CSF should be tested for the presence of group B streptococcal or E.coli K1 antigen, which gives accurate and prompt diagnostic information.

An LP should be performed 48 hours after the completion of antibiotic therapy. The last CSF may not show complete clearing of cells, but the sugar and protein value should be within the normal range, no organism should be seen, the CRP should have fallen to a normal value, and the culture should be negative.

A new development in the diagnosis of meningitis in neonates and infants is the measurement of cytokines such as interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) in the CSF[25]. A recent study found IL-6 to

be present in the CSF of each of 20 infants with bacterial meningitis and absent in all 20 infants without bacterial meningitis. In case of aseptic meningitis, IL-6 was found in half, but at only about 10% of concentration found in bacterial meningitis. More research is needed to define the predictive value of tests for neonatal meningitis based on cytokine measurements.

Acute-phase proteins

C-reactive protein

CRP is a better indicator of infection than the WBC indices, especially if serial measurements are made[26] and a receiver operator characteristic curve is constructed to establish the best cut-off value. It takes several hours for the CRP concentration to rise in an infected baby, however, and so the CRP is not often of much value in deciding whether to treat with antibiotics. The greatest worth of CRP is in the retrospective evaluation of a clinical diagnosis of sepsis after starting treatment. Culture grown sepsis is unlikely if the CRP does not rise within 24-48 hrs of the onset of the illness[27,28,29], and the combination of a normal CRP and negative cultures at 48 hours is a generally safe basis for stopping antibiotic therapy which was started on clinical suspicion. Serial measurements of CRP are useful in monitoring the progress of infection and may help decide for how long to continue treatment. Persistently elevated CRP

during antibiotic therapy for presumed bacterial infection should suggest the possibility of fungal infection, resistant organisms, or the development of a complication such as bacterial endocarditis or abscess formation. A raised CRP is often seen in association with meconium aspiration, even when there is no evidence of bacterial infection.

Other acute phase proteins

Orosomucoids (α1-acid glycoprotein), haptoglobin, α1-antitrypsin and α1-antichymotrypsin have all been used in assessing neonatal infection, but add little if anything to what is learnt from studying CRP. The same applies to fibronectin assays, although it is worth pointing out that any septic preterm infants develop significantly low plasma fibronectin concentrations, which may impair their ability to combat infection.

Serum Procalcitonin: Elevated serum concentrations of procalcitonin have recently been shown to predict neonatal sepsis with considerable accuracy. Procalcitonin distinguishes between infection and inflammation which CRP does not. It differentiates between bacterial and viral infection with high specificity. Procalcitonin a precursor of calcitonin, It contains 116 amino acids. It is secreted by C cells of thyroid gland in normal situation. In bacterial infection it is secreted by infected monocyte and macrophage. Bacterial lipopolysaccharide has been a potent inducer of PCT release in to systemic circulation. PCT level start to rise from 3 -

4 hrs after an endotoxin challenge and peak about 6 hrs. PCT has half life of 25 to 30 hrs[30].

Cytokines

TNF-α and IL-6

Since TNF-α is a principal indicator of systemic inflammation and together with IL-6 induces CRP, elevation of TNF-α and IL-6 concentrations in plasma should provide an early indication of sepsis. IL-8 is also likely to be an early indicator of sepsis, as it is involved in neutrophil release from the bone marrow and neutrophil activation. The value of these cytokines as markers of bacterial sepsis is in newborn infants has recently been reviewed[31].

It appears that IL-6 is a better marker of early-onset sepsis than CRP and that combining cytokine and CRP measurements, as well as serial testing, improves the accuracy of the tests as the markers of sepsis. Umbilical venous IL-6 (but not TNF-α) concentrations have been shown to be elevated in every preterm babies with intrauterine or early onset sepsis.

Serum granulocyte colony stimulating factor

Using a cut off value of 120pg/ml, the serum G-CSF concentration has been shown to have a sensitivity of 95%, a specificity of 73%, a positive

predictive value of 40% and a negative predictive value of 99% in the diagnosis of culture proven neonatal sepsis[32].

Immunological studies

Antigen detecting tests

Counter immune electrophoresis has been used to detect the presence of bacterial antigens in blood, urine or CSF, but it is little used in neonatal practice. However, rapid screening for GBS using latex particle agglutination is in quite widespread use for detecting both maternal and neonatal colonization. In screening neonates, it has been suggested that it may be best to concentrate the urine before testing. However a recent evaluation of the test on concentrated urine in screening fort GBS within the first 24 hours of life found a sensitivity of 90%, a specificity of 70%, a positive predictive value of 12% and a negative predictive value of 99%[33]. These results suggest that the main value of the test may be in providing reassurance of the absence of GBS.

Genetic techniques

It is now possible to amplify highly conserved DNA sequences from a variety of Gram-positive and Gram-negative organism, as well as many viruses, using PCR, while avoiding the simultaneous amplifications of associated human DNA[34]. This method has the potential to be automated

and to provide rapid diagnosis of bacteraemia. Other DNA amplification techniques are also becoming available.

Gastric aspirate

This can be viewed as a sample of amniotic fluid, plus or minus some swallowed secretions from the birth canal. About one-third of gastric aspirates show bacteria on gram stain (often potential pathogens, such as the Enterobacteriaceae, GBS and Enterococci) and a similar proportion contain some polymorphs. The great majority of these babies do not become septic, and the results of gastric aspirate microbiology cannot be considered an argument for antibiotic therapy. If a baby is thought to be infected on clinical grounds, however, it is important to choose antibiotic therapy that will cover any organisms seen in gastric aspirate. The gastric aspirate can only contribute to the diagnosis of infection if taken immediately after birth and before the baby has been fed.

Maternal high vaginal swab

When babies present with signs of infection within the first 24-48 hours of birth, the source is likely to be the maternal vagina, and a high vaginal swab (HVS) may well grow the responsible organism. However a low vaginal/perinial swab with enrichment media is more likely to yield a positive result for GBS. In common with the gastric aspirate and surface

swabs, however, the HVS tells about possible exposure to pathogens and not about infection, and the results are available too late to influence initial decision-making about therapy. They may help, though, to decide about the need to continue with therapy and on the choice of therapeutic agent.

Urine

There are two practical ways to obtain urine from babies for the purpose of diagnosing infection. One is to use a urine collection bag and the other is to perform a suprapubic aspiration (SPA). SPA overcomes the problem of contamination, and pus cells or organisms in a technically satisfactory SPA indicate urinary infection. To avoid delay and uncertainty, it may be worth performing an SPA in the initial assessment of the sick baby who is thought to be septicemic.

As part of the routine septic screen it is usual to begin with a urine specimen collection bag applied to the perineum. The perineum should be cleaned carefully before the bag is applied, and the bag should be removed as soon as the urine is passed. If bacteria and white cells are seen this strongly suggests UTI. Positive bag urines should always be viewed with suspicion unless there are many white cells (>150/cumm) and a pure growth of at least 10^8 organisms per liter of urine (10^5/ml). A mixed growth or an organism other than E.Coli, obtained from bag urine

should always be confirmed by performing an SPA. It is also possible to screen for UTI in babies by means of dipsticks. These measure the concentrations of leukocyte esterase, nitrites and protein by a colour change which can be read using a photometer. One study has shown a negative predictive value for UTI of 99.4% in a cohort of newborn babies and infants[35].

Tracheal secretions and endotracheal tube tip culture

The results of cultures of respiratory secretions should therefore be used to inform the choice of antimicrobial agents for suspected pulmonary infection. However it is naive to base the diagnosis of pulmonary infection solely on the results of culture of respiratory secretions as illustrated by a recent study comparing tracheal aspirate cultures from babies showing signs of respiratory deterioration with cultures from babies who were stable. No significant difference was found in the rate of positive cultures for bacteria, viruses, Chlamydia or Ureaplasmas. Cultures were positive in about one-third babies in each group[36].

Vascular lines and thoracentesis tube

The tips of umbilical cannulae, central lines and thoracentesis tubes should be sent for culture when removed. Central lines can be cultured using the 'Macki roll' technique in which the line is rolled across the

culture plate and a subsequent colony count performed. This can help to distinguish genuine line infection from skin contamination during removal of the line.

The 'sepsis screen'[6]

Parameter	Abnormal value
Total leukocyte count	<5000/cubic mm
Absolute neutrophil count	Low count as per Manroe chart for term infants and Mouzinho chart for VLBW babies
Immature(band cells) to total neutrophil ratio	>0.2
Micro-ESR	>15mm 1st hour
C-reactive protein (CRP)	> 1mg/dl

Table:2

A battery of above indirect markers of infection when collectively studied provides an extremely reliable index of neonatal sepsis and serves as a useful guide for initiating antibiotic therapy. When at least two of the indirect markers of infection are positive, it gives the sensitivity and specificity of 93 % and 88% respectively.

The septic screen is indicated at birth if an infant is born following prolonged rupture of membranes, foul smelling liquor, peripheral maternal fever and severe birth asphyxia with active resuscitation. After

birth if baby develops RDS or non specific features of neonatal sepsis, septic screen is indicated to support or refute the clinical suspicion so that unnecessary antibiotic usage is curtailed during neonatal period.

Sepsis screen is considered as positive when 2 or more parameters are positive. When initial screen is negative, the diagnosis of sepsis can be excluded with reasonable certainty. In early onset sepsis, polymorphs in the gastric aspirate as a marker of chorioamnionitis can be used as an additional parameter of sepsis screen.

Treatment

There should be low threshold for starting antibiotic therapy, pending the results of culture and other tests. Antibiotics should be given through intra venous route, in appropriate dose at appropriate intervals for the age and gestation of the baby. The wide range of potential pathogens and the propensity of some of the common bacteria to possess or acquire antibiotic resistance make the choice of antibiotics difficult.

The initial choice is guided by three considerations. Knowledge of the species of bacteria most likely to cause infection in the particular unit. This knowledge is best acquired by the formal collection of data by the department of microbiology in the hospital. Knowledge of antibiotic resistance pattern of bacteria, most likely to be responsible for the

infection, these vary from unit to unit and with in particular unit over time, mainly as a result of antibiotic use[37]. Knowledge of patient's previous antibiotic therapy. This is important because previous antibiotic therapy predisposes to infection with multi drug resistant organism.

Initial therapy

The choice of antibiotic for gram negative bacilli rests between an aminoglycoside and a third generation cephalosporin, such as ceftazidime, and should be based on local knowledge antibiotic resistance, the site of infection and toxicity of particular combinations. If Pseudomonas species are suspected ceftazidime should be used in preference to cefotaxime. Although a combination of vancomycin and either a third generation cephalosporin or an aminoglycoside will cover the majority of infections in neonatal unit, a definitive choice can only be made if the organism is identified and its susceptibility pattern is established. Many newer antibiotics are finding a useful role in difficult cases. Aztreonam is valuable in the treatment of gram negative sepsis. Meropenem is proving to be a good second line drug.

Definitive antibiotic therapy

Once the infecting organism is identified, therapy is rationalized to maximize efficacy and to minimize the risk of inducing resistance.

The following are suitable antibiotic choices for the common neonatal pathogens.

CONS: Vancomycin is the current drug of choice. The strains of CONS responsible for sepsis among babies on a NICU are commonly insensitive to penicillin, cloxacillin and gentamycin. Routine susceptibility testing sometimes indicates that a CONS resistant to methicillin is sensitive to cephalosporins, but cross resistance is common and all CONS that are resistant to penicillinase resistant penicillin should be considered resistant to cephalosporins. Persistent infection with CONS despite vancomycin therapy has been treated successfully with a combination of vancomycin and rifampicin[38].

Staph aureus: Anti staphylococcal penicillin, such as cloxacillin, should be used in preference to vancomycin if the organism is sensitive. For Methicillin resistant staph aureus (MRSA) vancomycin is currently the drug of choice although there is evidence of a spectrum of decrease vancomycin susceptibility among staphylococcal isolates. Persistent infection with MRSA despite vancomycin therapy has been treated successfully with a combination of vancomycin and rifampicin. An alternative treatment is with the recently introduced antibiotic known as linezolid. The usual dose for babies is 10mg/kg twelfth hourly.

E.coli: An aminoglycoside or a third generation cephalosporin, depending on sensitivity pattern should be used

Klebsiella: An aminoglycoside or a third generation cephalosporin, depending on sensitivity pattern should be used

Enterobacter, Citrobacter, Serratia and Pseudomonas: An aminoglycoside and a third generation cephalosporin in combination should be used. Ceftazidime should be used if Pseudomonas is suspected.

Enterococci: Ampicillin or vancomycin plus an aminoglcoside should be used.

Combination therapy is recommended partly to exploit synergistic antibiotic combinations and partly to prevent the emergence of antibiotic resistance.

Duration of antibiotic sepsis in neonatal sepsis

Diagnosis	Duration
Culture and sepsis screen negative but clinical picture suggestive of sepsis	5-7 days
Sepsis screen positive but blood/CSF culture negative	7-10 days
Blood culture positive but no meningitis	10-14 days
Meningitis(irrespective of culture report)	21 days
Arthritis, osteomyelitis, endocarditis	4-6 weeks
Ventriculitis	6 weeks

Table: 3

Meningitis

The safest initial blind treatment for suspected early-onset meningitis is still probably a combination of ampicillin and an aminoglycoside. This will effectively begin to treat meningitis caused by GBS, L.monocytogenes, Enterococci, H.influenza and many gram negative organisms. The alternative choice is a third generation cephalosporin, such as cefotaxime or ceftriaxone, plus ampicillin. A combination of third generation cephalosporin and an aminoglycoside is sometimes used, but this will not effectively treat L.monocytogenes or Enterococci. For late onset cases the blind choice is more difficult, but the combination of a

third generation cephalosporin and an aminoglycoside probably offers the best chance of immediately effective therapy.

GBS should be treated with benzylpenicillin plus or minus gentamicin with which there is some synergy. L.monocytogenes and Enterococci are treated with ampicillin and gentamicin. Gram negative bacilli vary so much in their sensitivity patterns that definitive therapy can only be decided after the microbiology department has carried out sensitivity testing. This is especially so in the case of nosocomial infections among the inmates of a NICU, who may acquire some very unusual and resistant pathogens. Antibiotic therapy for neonatal meningitis should be continued intra venous for at least 21days.

Bone and joint infection

Vancomycin and a third generation cephalosporin is a reasonable starting point until the results of blood cultures are available. Thereafter the appropriate antibiotics should be given i.v. for at least 4-6 weeks. When pus is obtained at aspiration, orthopaedic advice should always be sought about surgical drainage of the bone or joint.

Urinary tract infection

The usual antibiotic combinations for either early or late onset sepsis should be used and the treatment refined when the results of cultures are

available. If UTI is confirmed antibiotics should be continued for 10-14 days. Resolution of infection should be confirm with further urine cultures. Once the infection has been treated, prophylaxis with low dose trimethoprim, given in a single dose at night, should continue until radiological investigations have excluded underlying abnormalities. If the investigations are normal, prophylaxis can be discontinued, but the infant should be followed with urinalyses every 3 months for at least a year. If there is evidence of reflux antibiotic prophylaxis should be continued. UTI due C.albicans has traditionally been treated with amphotericin alone or in combination with one of the newer antimycotic drugs. A recent report has suggested that results can also be obtained with a combination of fluconazole and flucytosine.

Listeriosis

The most effective antibiotic therapy is ampicillin plus gentamicin and in units where Listeria is a common pathogen; there it is must to be said for using this combination as the routine for early onset sepsis. Listeria is resistant to all third generation cephlosporins. Intrathecal treatment is not required for listerial meningitis.

Adjunctive therapies

Prophylactic use of immunoglobulin: Preterm infants have lower serum IgG concentrations than their term counterparts and show a progressive fall in IgG concentration for many weeks after birth. Unsupplemented, about 15% of VLBW babies will develop IgG concentrations less than 200mg/dl by about 12 weeks of age[39]**.** There is evidence that VLBW babies who develop hospital-acquired infection have significantly lower serum IgG concentrations than those who do not[40]**.** It was found that if the serum IgG was less than 350mg/dl during the first week or less than 230mg/dl in the second week, the risk of sepsis was five times greater than among babies with higher levels.

It is possible to maintain IgG concentrations in these infants by giving regular infusions of immunoglobulin. Numerous studies have looked into this, and 19 of them have recently been the subject of an independent meta-analysis[41]**.**The main findings were that the prophylactic use of immunoglobulin resulted in a 3% reduction in sepsis and a 4% reduction in any serious infection. There was no significant effect on mortality.

Fresh frozen plasma (FFP): It is commonly used in the treatment of the septic infant in an attempt to increase humoral immunity. Adult FFP increases neonatal neutrophilic chemotaxis in vitro[42]**.** When infants were

infused with FFP, there was no effect on the serum concentrations of components of humoral immunity.

Exchange transfusion: It provides humoral factors and removes some noxious products of septicemia, like bacterial toxins, fibrin degradation products and cytokines. Some studies have suggested that exchange transfusion with fresh whole blood is useful in neonatal sepsis[43].

Granulocyte transfusion: Granulocytes obtained from plasmapheresis or from donor blood have been given to septic babies, particularly when their illness has been complicated by neutropenia. The most recently published randomized trial has suggested a possible benefit, but overall the literature is not convincing.

Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: G-CSF and GM-CSF are crucial in inducing granulocyte production and activation in the newborn during sepsis, and may be a useful marker of infection. The mononuclear cells of the newborn are less able to generate G-CSF than those from adults[44], and this may partly explain granulocytopenia that often accompanies severe neonatal sepsis. In human newborns, many trials of recombinant G-CSF and GM-CSF in suspected sepsis have proven an increase in neutrophil counts and increased functional activity, as judged by C3bi expression. There are now many published studies on the influence of G-CSF and

GM-CSF on outcome in neonatal sepsis when used either in treatment or prophylaxis. An almost universal finding has been a marked rise in the neutrophil count, and no acute toxicities have been noted. Evidence of efficacy in decreasing mortality rates or other important outcome measures is not yet clearly proven and almost all published reports state the necessity for bigger and more definitive work.

Pentoxifylline (oxypentifyline)

It is an immunomodulating agent which can augment impaired neutrophil function in newborn infants. It has a wide range of effects, including increasing nitroblue tetrazolium reduction, altering neutrophil deformability and increasing H2O2 production[45]**.** Its use in septic infants has not been established.

Nutrition

Babies with septicemia are usually catabolic but rarely tolerate enteral feeds, because of a paralytic ileus, NEC or gastroenteritis. Intravenous feeding, particularly fat is poorly tolerated during septicemia. Due to this reason dextrose and electrolytes alone should be used for first 1 to 2 days of infection. More complete parenteral or enteral nutrition should be given as soon as there is improvement in the baby's condition.

REVIEW OF LITERATURE

Alireja Abdollahi et al conducted study on diagnostic value of simultaneous measurement of procalcitonin, interleukin-6 and hs-CRP in prediction of early onset neonatal sepsis in Vali-e-Asr hospital affiliated to Tehram university of medical science, Iran. They conducted study in 95 neonates who were below 12hours of age and had clinical signs of sepsis or maternal risk factor for sepsis. Blood samples were obtained in first 12 hours of life and between 24-36 hours of life for determination of serum level of PCT, IL-6 and hs CRP. They concluded that the combination of PCT and IL-6 yielded sensitivity of 88%, while that of PCT and CRP was 82%. Neither combination being significantly higher than with PCT alone. Sensitivity of PCT (76%) compared with that of CRP (48%) was significantly different (p=0.011). PCT begins to increase in 2hours of sepsis onset and precedes the rise IL-6 and CRP[46].

Boo N Y et al conducted study regarding usefulness of a semi quantitative procalcitonin test kit for early diagnosis of neonatal sepsis in NICU of Hospital University Kebangsaan, kuala Lumpur, Malaysia. 87 infants were recruited, of which 18 were confirmed to have sepsis based on positive blood culture results. They concluded at a cut off level of greater than or equal to 2ng/ml, the sensitivity of PCT Q-kit in detecting neonatal sepsis at the onset of signs was 88.9% and its specificity was

65.2%. The sensitivity of CRP for diagnosis of sepsis was 55.6% and its specificity was 89.9%[47].

Daynia E Bellot et al done study on usefulness of serum procalcitonin as an early marker of neonatal sepsis in Neonatal unit, Johannesburg hospital, and microbiology laboratory National Health Laboratory Service (NHLS), South Africa. They conducted study in 183 infants admitted to NICU. They concluded PCT predicted 89.5% of definitive infection. Receiver Operating characteristic (ROC) curve analysis for PCT to predict definitive infection showed odds ratio (OR) 1.145 (95% confidence interval [CI] 1.05-1.25) with an area under curve of 0.778. PCT had a negative predictive value of 0.95 (95% CI 0.915-0.988) for definitive infection[48].

Claudio chiesa et al conducted study on Reliability of Procalcitonin concentration for the diagnosis of sepsis in critically ill neonates in The Institute of Experimental Medicine, National Research Council and The Institutes of Pediatrics, Child Health and Hygiene, and Department of Experimental Medicine, University of Rome, Rome. Timed procalcitonin determinations were prospectively obtained during two postnatal period 0-48hours of age (period 1) and 3-30 days of age (period 2). In period 1 PCT level was measured in 83 healthy newborn and in 120 NICU patients. Analysis of pooled procalcitonin values

obtained for group1 patients over the 48hours period after birth yielded sensitivity of 92.6% and specificity 97.5%. In period 2, blood samples from 23 cases with systemic infections were analyzed for procalcitonin concentration at the onset of signs of infection showed sensitivity and specificity 100%[49].

Claudio chiesa et al conducted study on C - reactive protein, Interleukin-6 and procalcitonin level in the immediate postnatal period and the influence of illness severity, risk status, antenatal and perinatal complication and infection on it. The Score for Neonatal Acute Physiology (SNAP) was used to define illness severity, with SNAP Perinatal Extension (SNAP-PE) used to define the combined physiological and perinatal mortality risk. A total of 134 ill neonates were analyzed for the association of SNAP, SNAP-PE and maternal and perinatal variables with C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT) concentration at birth, 24 and 48 hours of life. They concluded that early onset neonatal infection was associated with significant increase in CRP, IL-6 and PCT concentration at all three points independent of illness severity. However in babies without infection, higher SNAP and SNAP_PE score were associated with higher IL-6 concentration at birth. PCT sensitivity and specificity was greater than that of CRP and IL-6[50].

N joram et al conducted study on Umbilical cord blood procalcitonin and C-reactive protein concentrations as markers for early diagnosis of very early onset neonatal infection. Procalcitonin (PCT) and C-reactive protein (CRP) concentrations in umbilical cord blood of 197 neonates were measured to evaluate their value as markers of infection. Sixteen of the neonates were infected. The sensitivity, specificity, and negative and positive predictive values were respectively 87.5%, 98.7%, 87.5%, and 98.7% for PCT and 50%, 97%, 67%, and 94% for CRP. Serum PCT in cord blood seems to be a useful and early marker of antenatal infection[51].

Ibeh Isaiah Nnanna et al had done a study on usefulness of serum procalcitonin as an early detection of neonatal bacteraemia and septicaemia in a tertiary health care facility. They conducted study in 60 neonates suspected to have sepsis. A total of 55 neonates showed a positive PCT test. An important finding was that PCT on day 0 was the only independent risk factor associated with previous infection, odds ratio= 7.69, 95% CI: 2.50- 25: $p< 0.001$. The diagnostic value of PCT evaluated through construction of corresponding ROC curves was 0.89 (95% CI, 0.79- 0.98) and positive and negative value reached 91.6% and 80% respectively. When compared with body temperature, leucocyte count and CRP, PCT was the most accurate marker for infection[52].

Yadolla Zahedpasha et al conducted study on Procalcitonin as a Marker of Neonatal Sepsis in Department of Pediatrics, Babol University of Medical Sciences, Babol, IR Iran. Thirty-eight neonates with clinical (n=8), suspected (n=19) and proven sepsis (n=11) were evaluated. The PCT levels were measured by immuno luminoassay before and on day 5 of treatment. PTC levels of 0.5-2 ng/ml, 2.1-10 ng/ml and >10 ng/ml were considered as weakly positive, positive, and strongly positive respectively. The result showed that the serum procalcitonin levels seem to be significantly increased in proven sepsis and decrease dramatically in all types of sepsis after appropriate treatment[53].

Vincenzo Maniaci, MD et al conducted study on Procalcitonin in Young Febrile Infants for the Detection of Serious Bacterial Infections in Division of Emergency Medicine and Department of Medicine, Children's Hospital Boston. A total of 874 patients, ≤90 days of age, with documented temperatures of ≥38 degree Celsius were evaluated during the 18-month study period. ROC curves for procalcitonin level were constructed by comparing patients with definite serious bacterial infections (SBIs) and those with no serious bacterial infection (no SBI). In comparing definite SBIs and no SBI, the ROC area under the curve (AUC) was 0.82; a cut off value of 0.13 ng/mL yielded sensitivity of 96.7% (95% CI: 81.0%–99.8%), specificity of 30.3% (95% CI: 24.0%–

37.5%), NPV of 98.3% (95% CI: 89.7% –99.9%), and negative likelihood ratio of 0.11 (95% CI: 0.02–0.76)[54].

Procalcitonin in preterm infants during the first few days of life: Introducing an age related normogram conducted by **D Turner** et al in neonatal intensive care unit at Shaare Zedek Medical Center, a University affiliated hospital in Jerusalem, Israel. The suggested neonatal normograms of preterm infants are different from those of term infants. Procalcitonin concentrations exceeding the 95th centile may be helpful in detecting congenital infection, but not at birth[55].

An update on the use of C-Reactive Protein in early-onset neonatal sepsis: Current insights and new tasks by **Nora Hofer et al** at Research Unit for Neonatal Infectious Diseases and Epidemiology, Medical University of Graz. The delayed induction of the hepatic synthesis of CRP during the inflammatory response to infection lowers its sensitivity during the early phases of sepsis. The performance of serial determinations 24–48 hrs after the onset of symptoms is recommended; as it clearly improves diagnostic accuracy.CRP is particularly useful for monitoring the response to treatment and for ruling out an infection. A repeated determination of CRP 24–48 hrs after the initiation of antibiotic therapy has been reported to carry a 99% negative predictive value in accurately identifying uninfected neonates, though nothing replaces a

clinical impression and the gold standard. CRP values undergo a physiological 3-day rise after birth. This physiologic dynamics as well as certain maternal and perinatal factors may affect interpretation of what constitutes 'normal' CRP values in healthy neonates. Furthermore, some reports suggest noninfectious confounders such as meconium aspiration syndrome and perinatal maternal risk conditions may significantly elevate CRP values in symptomatic or at-risk neonates and thus confound interpretation of CRP values in the diagnosis of sepsis[56].

Bacteriological Analysis of Blood Culture Isolates from Neonates in a Tertiary care hospital in India done by **Ghanshyam D et al** in Department of Pediatrics and Department of Microbiology, University College of medical Sciences and GTB Hospital, New Delhi. In total, 823 blood cultures from neonates were evaluated. Gram-positive cocci (309/823, 37.5%), Gram-negative bacilli (492/823, 59.8%), and Candida species (20/823, 2.43%) were grown. Staphylococci and Klebsiellae were the most common Gram-positive and Gram-negative organisms together accounting for 32.3% (266/823) and 33.8% (278/823) of the isolates respectively. Other common Gram-negative isolates were Enterobacter (62/823, 7.5%) and Escherichia coli (38/823, 4.6%)[57].

Kurien Anil Kuruvilla et al from the Department of Neonatology and Microbiology, Christian Medical College Hospital, Vellore, Tamil Nadu, India conducted study on bacteriological profile in sepsis in neonates in South India. They concluded that the incidence of neonatal bacterial sepsis is 9.8 per 1000 live births. E. coli- and Klebsiella were the most common organisms causing EOS and LOS, respectively. Enterococcus fecalis was also a major pathogen, both in EOS and LOS[58].

The effect of neonatal sepsis on platelet count and their indices conducted by **Abdalla Alshorman et al** in Princess Rahmah Teaching Hospital, Irbid, Jordan. Neonatal sepsis was diagnosed in 105 cases was included in the study. Thrombocytopenia was present in 45(42.8%) of the all cases of neonatal sepsis, of which 27 (60%) were found among gram negative sepsis. The remaining 18(40%) cases were due to gram-positive microorganisms. 19 (42.2%) of the cases of thrombocytopenia are premature babies and 26(57.8%) are full term babies[59].

JUSTIFICATION OF THE STUDY

Neonatal sepsis is the most important cause of neonatal mortality & morbidity, especially among low birth weight and preterm babies. Early recognition, diagnosis and treatment of serious infections in the neonates are essential. Progression from mild symptoms to death can occur in less than 24hrs. Most neonatal bacterial infections have an early bacteraemia phase preceding the development of a full blown septicemia or localization of infections in organs and tissues. During this phase the clinical signs are subtle, but this is when treatment must be started if there is to be intact survival. Early detection of neonatal systemic infection is difficult because the symptoms and signs of bacterial infection are nonspecific and similar to symptoms of non infectious process like respiratory distress syndrome and IEM. Though the blood culture is the gold standard test for sepsis, it takes longer time to get the results. The sensitivity of blood culture is less and is influenced by antibiotic use. Hence we need markers which can be performed as a screening procedure to predict sepsis at the earliest. In our setup we use WBC count and CRP value for early detection of sepsis. Interpretation of WBC count is difficult because of wide range of normal value in infants (5000 – 20000). CRP is a nonspecific inflammation and tissue necrosis. It is also elevated in noninfectious causes like respiratory distress syndrome and meconium

aspiration syndrome. CRP level do not rise significantly until 24 – 48 hrs of illness leading to false interpretation when sample is drawn early in the course of illness.

Recently procalcitonin (PCT) has been found to be useful marker in early diagnosis of bacterial infection. Bacterial lipopolysaccharide has been a potent inducer of PCT release in to systemic circulation. PCT level starts to rise from 3 - 4 hrs after an endotoxin challenge and peaks about 6 hrs. PCT has half life of 25 to 30 hrs. If we are able to measure PCT at the onset of infection we can initiate specific treatment without waiting for Culture results. In this study we aimed to find out the sensitivity of PCT as an early marker of neonatal sepsis and to compare CRP, WBC count and platelets with PCT in early detection of neonatal sepsis.

OBJECTIVES

Primary objective:

Procalcitonin as an early and reliable marker of neonatal sepsis

Secondary objective:

To compare the effectiveness of CRP and WBC with procalcitonin in predicting the neonatal sepsis at the earliest

METHODOLOGY

Study design: Validation of diagnostic test

Study place: NICU, Coimbatore medical college and hospital (CMCH).

Study period: Dec 2011 to Sep 2012

Study population: All neonates admitted in NICU, in CMCH with risk of sepsis or suspected sepsis either at admission or during the course of admission during the study period

Inclusion criteria:

- Neonates with risk of early onset sepsis
    1. PROM > 18 hours
    2. MRO > 12 hours
    3. Maternal fever during perinatal period
    4. Foul smelling liquor
- Neonates admitted with Signs and symptoms S/O sepsis both EOS and LOS
    1. Feeding intolerance
    2. Lethargy
    3. Temperature instability
    4. Apnea and respiratory distress

5. Poor perfusion
6. Seizure
7. Tachycardia
8. Abdominal distension

Exclusion criteria:

- Newborn already started on antibiotics

Sample size: 49

Sample size estimation formula - $Y = \mu1-\mu2/ \sigma$

Y - The difference between the two population means

σ - Population standard deviation

Based on Previous studies $\mu1= 5.49$

$\mu2= 5.21$

SD or $\sigma = 0 .56$

$Y = 0.50$

Corresponding to Power at 0.50 at $\acute{\alpha}$ 0.70, the estimated sample size is 49.

Sampling technique: All consecutive neonates fulfilling inclusion criteria were studied until the sample size was achieved.

DEFINITIONS

Culture positive sepsis: Neonates whose blood culture showed growth of the organisms.

Culture negative sepsis: Neonates whose blood culture showed no growth of the organisms, but had other positive investigations suggesting sepsis.

Early onset sepsis: Neonates who developed features of sepsis within 72hrs of life.

Late onset sepsis: Neonates who developed features of sepsis after 72hrs of life.

Normal values: Procalcitonin - <0.05ng/dl

CRP – 0.5mg/dl

WBC – 5000 – 20000/cumm

Platelet count – 1-5lakhs/cumm

2×2 Table[60]

Screening test	Diagnostic test		Total
	Positive	Negative	
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Table:4

- **Sensitivity**: probability that a test result will be positive when the disease is present (true positive rate). It is calculated by the formula a /a+c × 100.

- **Specificity**: probability that a test result will be negative when the disease is not present (true negative rate). It is calculated by the formula d /b+d × 100.

- **Positive likelihood ratio**: ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease, i.e. True positive rate / False positive rate = Sensitivity / (1-Specificity)

- **Negative likelihood ratio**: ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease, i.e. False negative rate / True negative rate = (1-Sensitivity) / Specificity
- **Positive predictive value**: probability that the disease is present when the test is positive. It is calculated by the formula a /a+b × 100.
- **Negative predictive value**: probability that the disease is not present when the test is negative. It is calculated by the formula d /c+d × 100.

Maneuver

50 newborns fulfilling inclusion criteria were enrolled. Consent was obtained from the parents. Relevant data including risk factors, clinical condition, were entered in preformed proforma. Before initiation of antibiotic therapy, blood sample for blood culture, CRP, PCT and WBC were obtained from peripheral vene puncture. Results will be interpreted and compared as follows: Culture positivity was taken as gold standard. PCT, CRP and WBC sensitivity, specificity, positive predictive value and negative predictive values were calculated by 2×2 table. Efficacy CRP

and WBC levels were compared with that of PCT in predicting neonatal sepsis.

Analysis was done using software MedCalc software – version 15.

Methods

CBC: Calculated by autoanalyser

Blood culture: 0.5ml of blood was collected in a container containing 5ml of Brain Heart Infusion Broth. It was incubated over 48 hours at 35-37 degree Celsius and plated on Mc Conkey agar and blood agar. Growth was checked after 24 hours.

CRP assay: Done in Immuno lab at Coimbatore by Immunoturbidimetric method. In this the serum sample is reacted with the buffer and anti-CRP coated latex. The formation of antibody-antigen complex during the reaction results in increase in turbidity. The extent of turbidity was measured as the amount of light absorbed at 570nm. By constructing a standard curve from the absorbance standards, CRP concentration of the sample was determined. Value $\geq$ 1mg/dl was taken as positive as per lab standard.

Procalcitonin assay: It was done at Immuno lab at Coimbatore by enzyme linked fluorescent assay (ELFA). The assay principle consists of one strip immune assay sandwich procedure with a final fluorescent detection. The solid phase receptacle (SPR) acts as a solid phase, as well as the pippeting device for the assay. Materials for the assay are ready to use and pre dispensed in the sealed reagent strips. All of the assay steps were done automatically by the instruments. The serum sample was put in the wells containing anti-procalcitonin antibodies coated with alkaline phosphatase (conjugate). The mixture of the sample and conjugate was passed in and out of the SPR several times. This procedure enables the antigen to combine with the immunoglobulin fixed to the interior wall of SPR and the conjugate to make a sandwich. Unbound substances were eliminated during washing.

Two detection procedures were performed successfully. During each step, the substrate (4-methyl-umbelliferyl phosphate) was passed in and out of SPR. The conjugate enzyme catalyses the hydrolysis of substrate into a fluorescent product, (4-methyl-umbelliferone). The fluorescence of which was measured at 450nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample.

At the end of the assay, the results were automatically calculated by the instrument in relation to the two calibration curves corresponding to two procedures and saved in memory, and then printed out. Value ≥ 2ng/dl was taken as positive as per lab standard.

RESULTS

A total of 50 neonates with features of sepsis were included in the study. Blood culture of 27 (54%) neonates showed growth of organism. Out of remaining 23(46%) neonates, 15(30%) had other positive investigations supportive of sepsis and termed as culture negative sepsis group. Rest of 8(16%) neonates had only clinical features of sepsis and no other supportive investigation for sepsis and termed as suspected sepsis.

The data obtained were analyzed as follows:

1. Features of study population (gestational age, birth weight, postnatal age, sex)
2. Percentage of early onset and late onset sepsis in study population
3. Organisms causing neonatal sepsis and its frequency.
4. Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio for procalcitonin, CRP, WBC count and platelet count.
5. Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio for combination of tests included in the study.
6. Receiver operated characteristic (ROC) curve for comparing the efficacy of PCT, CRP and WBC count.

7. Association between sampling interval with PCT & CRP level by partial correlation.

DESCRIPTIVE ANALYSIS

GESTATIONAL AGE DISTRIBUTION (WEEKS)

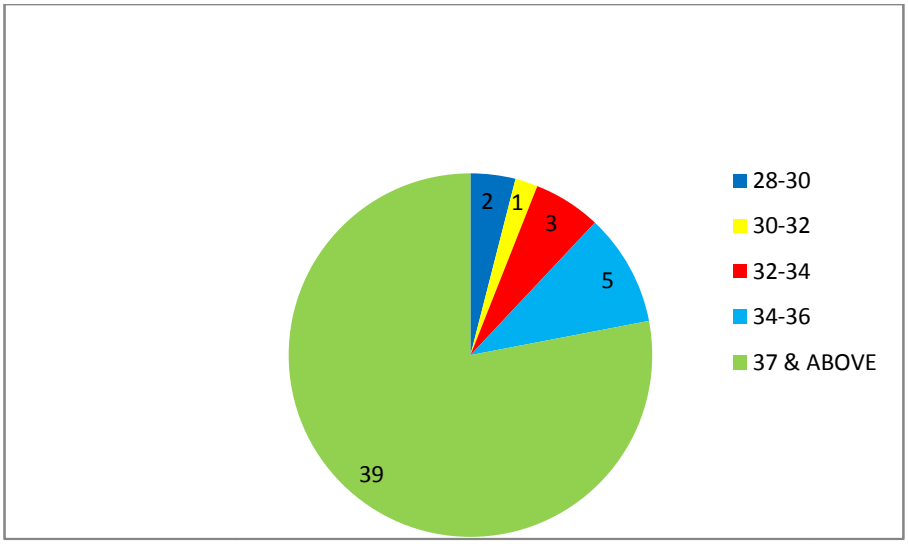

Figure 1: distribution of gestational age in study population

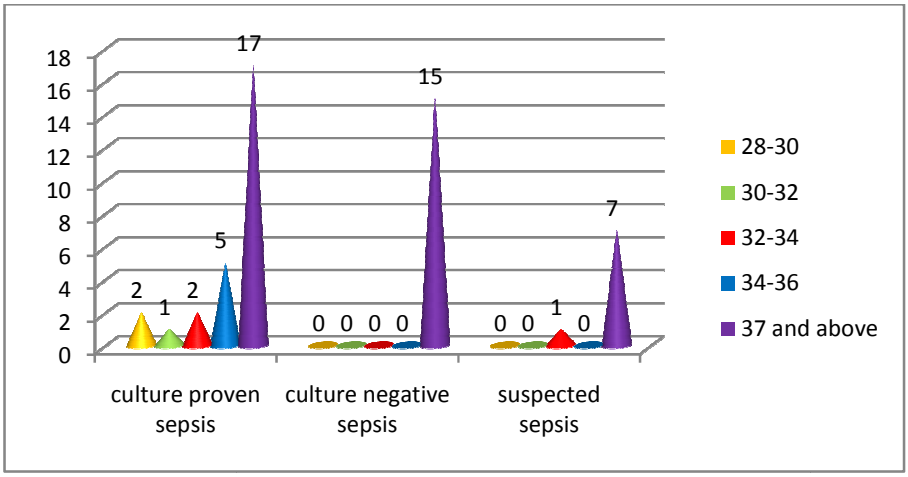

Figure 2: distribution of gestational age in study population among three groups

Out of 50 neonates included in the study, 39 (78%) were term, 3 (6%) were between 32-34 wks, 2(4%) were between 28-30 wks and 1 was between 30-32wk

SEX DISTRIBUTION

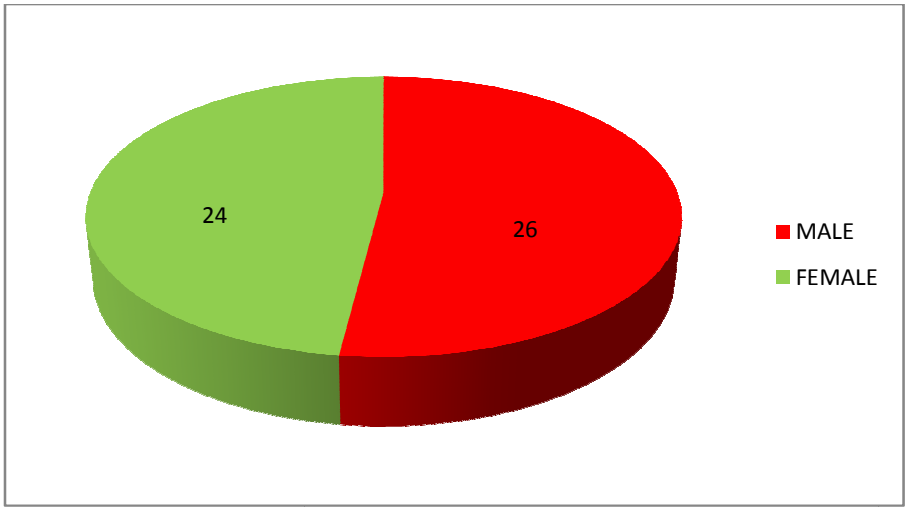

Figure 3: distribution of sex in study population

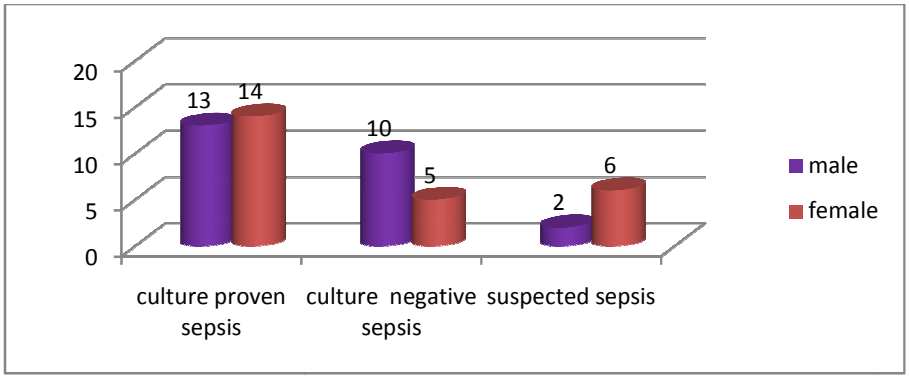

Figure 4: distribution of sex in study population among three groups

Out 50 neonates in the study 26 (52%) were male and 24 (48%) were female infants

WEIGHT DISTRIBUTION

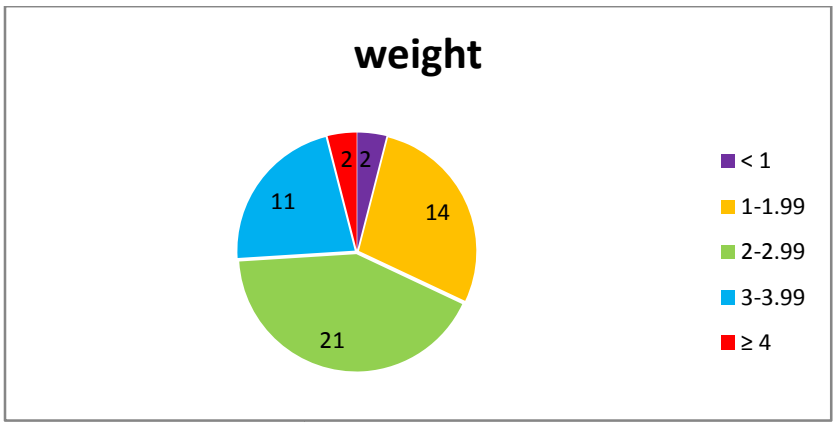

Figure 5: distribution of weight in study population

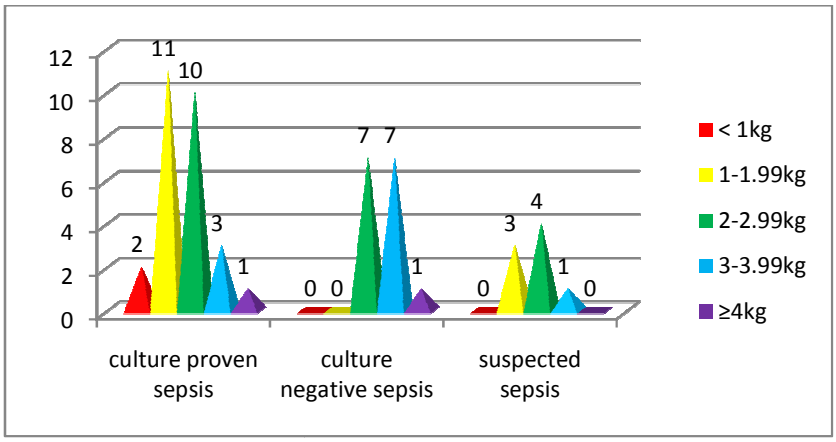

Figure 6: distribution of weight in study population among three groups

Out of 50 neonates 21(42%) weighed between 2-2.9kg, 14 (28%) weighed between 1-1.9kg, 11(22%) weighed between 3-3.9kg, 2(4%) weighed > 4kg and 2 weighed < 1kg

AGE DISTRIBUTION

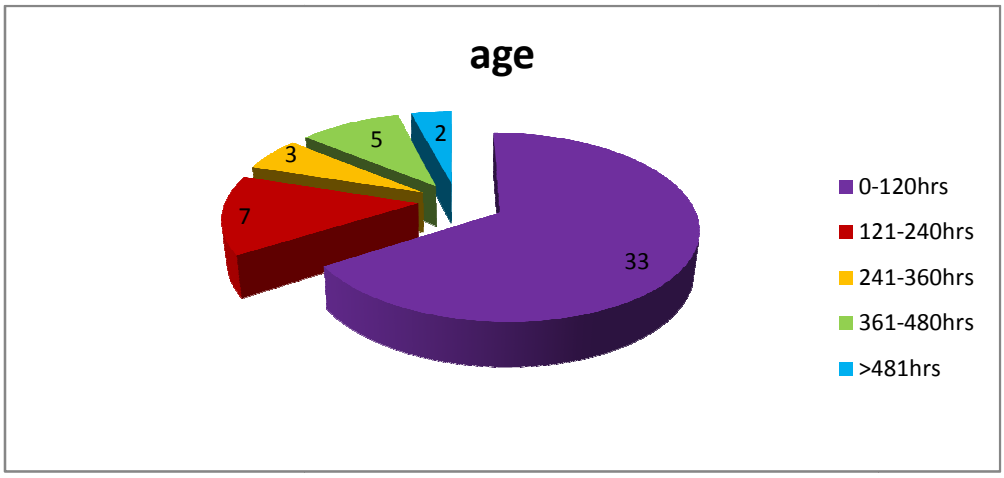

Figure 7: distribution of age in study population

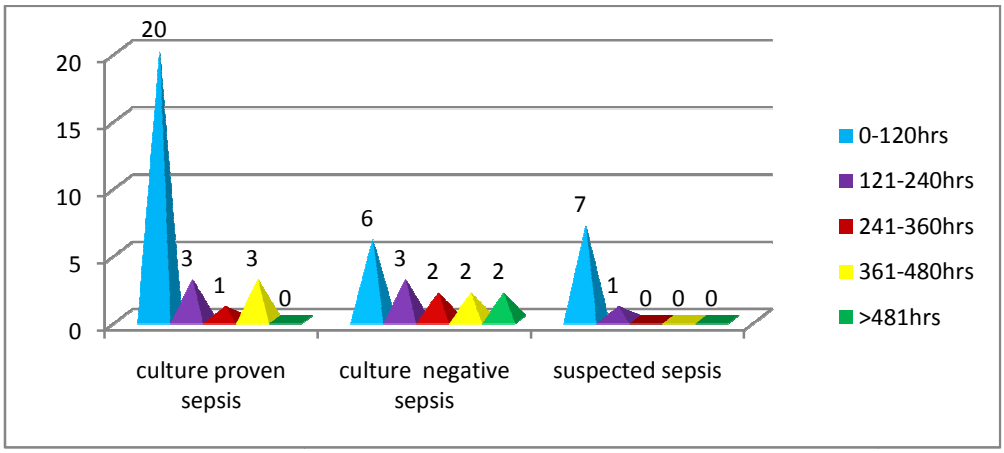

Figure 8: distribution of age in study population among three groups

Out of 50 neonates 27 (54%) were above 72 hours and 23 (46%) were below 72 hours

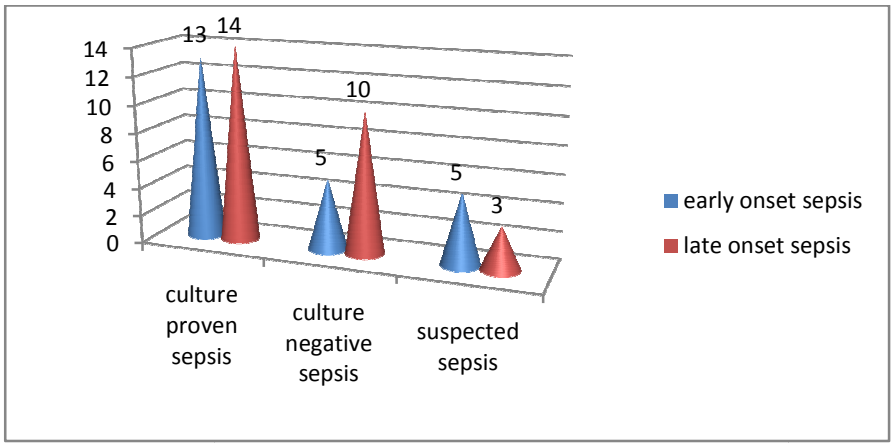

Figure 9: distribution of LOS & EOS in study population among three groups

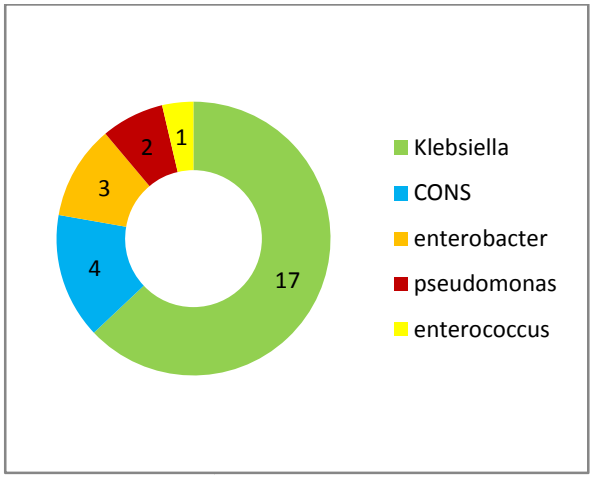

Figure 10: frequency of organism causing sepsis in study population

Out of 27 positive blood culture , Klebsiella pneumoniae was identified in 17(62.9%), Coagulase negative staphylococcus was identified in 4 cases (14.8%), Enterobacter spp was identified in 3 cases (11.1%), Pseudomonas was identified in 2 cases (7.4%) and Enterococcus was identified in 1 case (3.7%)

STATISTICAL ANALYSIS

Table: 5

PCT	Blood culture		Total
	Positive	Negative	
Positive	25	10	35
Negative	2	13	15
Total	27	23	50

Sensitivity - 92.59%

Specificity - 56.52 %

Positive Predictive Value - 71.4 %

Negative Predictive Value - 86.6%

Positive Likelihood Ratio - 2.13

Negative Likelihood Ratio – 0.13

Table: 6

CRP	Blood culture		Total
	Positive	Negative	
Positive	15	10	25
Negative	12	13	25
Total	27	23	50

Sensitivity – 55.55%

Specificity – 56.52 %

Positive Predictive Value – 60 %

Negative Predictive Value – 52 %

Positive Likelihood Ratio – 1.28

Negative Likelihood Ratio – 0.79

Table:7

WBC	Culture		Total
	Positive	Negative	
Positive	11	11	22
Negative	16	12	28
Total	27	23	50

Sensitivity – 40.74%

Specificity – 52.17 %

Positive Predictive Value – 50 %

Negative Predictive Value – 42.85 %

Positive Likelihood Ratio – 0.85

Negative Likelihood Ratio – 1.14

Table:8

Platelet	Culture		Total
	Positive	Negative	
Positive	10	3	13
Negative	17	20	37
Total	27	23	50

Sensitivity – 37.03%

Specificity – 86.95 %

Positive Predictive Value – 76.92 %

Negative Predictive Value – 54.05 %

Positive Likelihood Ratio – 2.84

Negative Likelihood Ratio – 0.72

Table:9

CRP/WBC	Culture		Total
	Positive	Negative	
Positive	21	13	34
Negative	6	10	16
Total	27	23	50

Sensitivity – 77.77%

Specificity – 43.47%

Positive Predictive Value – 61.76 %

Negative Predictive Value – 62.5%

Table:10

CRP /WBC/Platelets	Culture		Total
	Positive	Negative	
Positive	22	14	36
Negative	5	9	14
Total	27	23	50

Sensitivity – 81.48%

Specificity – 39.13%

Positive Predictive Value – 61.11 %

Negative Predictive Value – 64.29%

Table:11

Procalcitonin/ CRP	Culture		Total
	Positive	Negative	
Positive	27	15	42
Negative	0	8	8
Total	27	23	50

Sensitivity – 100%

Specificity – 34.78%

Positive Predictive Value – 64.28%

Negative Predictive Value – 100%

Table:12

Procalcitonin/ WBC	Culture		Total
	Positive	Negative	
Positive	25	15	40
Negative	2	8	10
Total	27	23	50

Sensitivity – 92.59%

Specificity – 34.78%

Positive Predictive Value – 62.5%

Negative Predictive Value – 80%

Table:13

Procalcitonin/ Platelets	Culture		Total
	Positive	Negative	
Positive	26	1	27
Negative	1	22	23
Total	27	23	50

Sensitivity – 96.29%

Specificity – 95.65%

Positive Predictive Value – 96.29%

Negative Predictive Value – 95.65%

Table:14

Procalcitonin/ WBC/CRP/Platelets	Culture		Total
	Positive	Negative	
Positive	27	17	44
Negative	0	6	6
Total	27	23	50

Sensitivity – 100%

Specificity – 26.08%

Positive Predictive Value – 61.36%

Negative Predictive Value – 100%

COMPARISION OF PCT, CRP & WBC

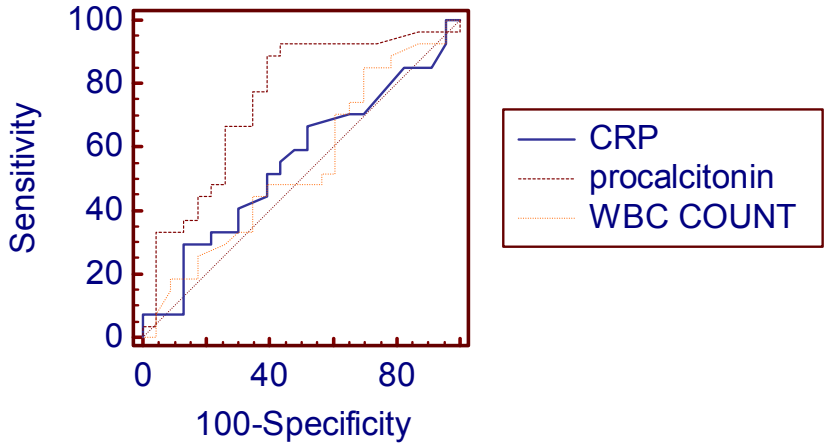

Figure 11: Comparison of PCT,CRP and WBC count by ROC curve

Table:15

Comparison of ROC curves

Variable 1	CRP		
Variable 2	procalcitonin		
Variable 3	WBC COUNT		
Classification variable	culture		
Sample size			50
Positive group :	culture = 1		27
Negative group :	culture = 0		23
	AUC	SE	95% CI
CRP	0.552	0.0831	0.405 to 0.693
procalcitonin	0.748	0.0729	0.605 to 0.860
WBC_COUNT	0.539	0.0840	0.392 to 0.681

Table:16

Pair wise comparison of ROC curves

CRP ~ procalcitonin	
Difference between areas	0.196
Standard Error	0.107
95% Confidence Interval	-0.0134 to 0.405
z statistic	1.834
Significance level	P = 0.0466
CRP ~ WBC_COUNT	
Difference between areas	0.0137
Standard Error	0.131
95% Confidence Interval	-0.244 to 0.271
z statistic	0.104
Significance level	P = 0.9169
Procalcitonin ~ WBC_COUNT	
Difference between areas	0.209
Standard Error[c]	0.124
95% Confidence Interval	-0.0338 to 0.453
z statistic	1.687
Significance level	P = 0.0315

The difference between area under ROC curve for PCT and CRP was 0.196 and p=0.0466 ($p<0.05$) which means there is significant difference between the efficacy of PCT & CRP in predicting neonatal sepsis.

The difference between area under ROC curve for PCT and WBC was 0.209 and p=0.0315 ($p<0.05$) which means there is significant difference between the efficacy of PCT & WBC in predicting neonatal sepsis.

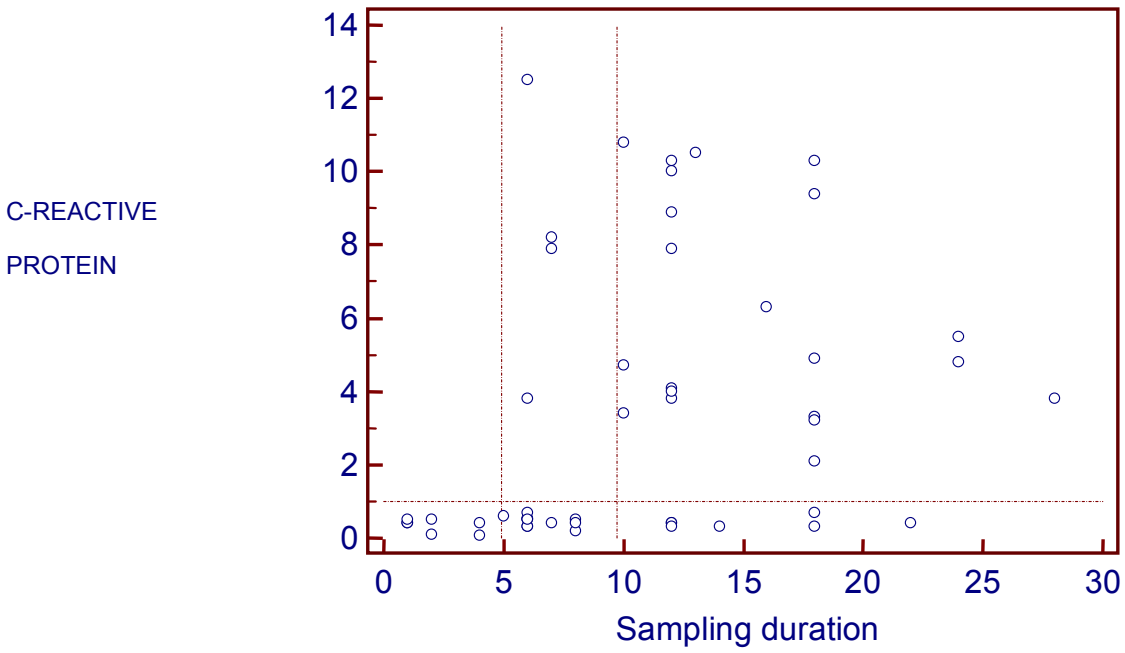

Figure 11: Scatter diagram between sampling interval and CRP level

Table:17

Partial correlation

Variable Y	c-reactive protein
Variable X	Culture
Covariates	sampling duration
Sample size	50
Correlation coefficient r	0.8641
Significance level	P=0.0067

Sampling interval has excellent correlation with CRP level, Pearson's correlation r=0.86 and p<0.05. Increased Sampling interval was associated with increased positivity for CRP.

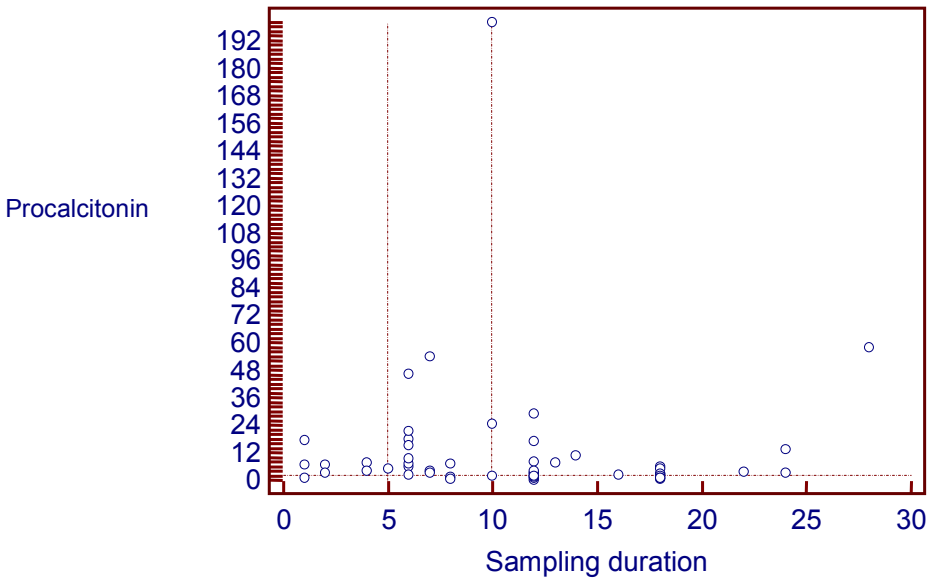

Figure 12: Scatter diagram between sampling interval and procalcitonin level

Table:18

Partial correlation

Variable Y	Procalcitonin
Variable X	Culture
Covariates	sampling duration

Sample size	50
Correlation coefficient r	0.5167
Significance level	P=0.0801

Sampling interval had no significant correlation with PCT level, Pearson's correlation r=0.516 and p>0.05.

DISCUSSION

The major cause of neonatal morbidity and mortality is neonatal sepsis. This study was conducted to show Procalcitonin can be used as an early and reliable marker of neonatal sepsis and to compare its efficacy with that of CRP and WBC count. These two tests are routinely used in our institution for initial sepsis screening. If CRP and WBC count are as efficacious as procalcitonin, they can be substituted for procalcitonin in resource poor setting and cost effective.

This study was conducted in 50 neonates who had clinical features of sepsis. Both preterm and term neonates were included. Both early onset sepsis and late onset sepsis were included. Blood samples were drawn for CRP, PCT, WBC count and blood culture before starting antibiotics. Other investigations like CSF analysis, CXR were done in symptomatic infants.

Out of 50 neonates blood culture was positive in 27 (54%) neonates.15 out of remaining 23 infants had other positive investigations like CSF analysis, CXR supporting sepsis and hence grouped as culture negative sepsis. Remaining 8 neonates had only clinical features and hence termed as suspected sepsis. Procalcitonin was positive (≥2ng/dl) in 35 neonates,

CRP was positive (≥1mg/dl) in 25 neonates and WBC count was positive (<5000 or > 20,000) in 22 neonates.

Sensitivity, specificity, positive predictive value and negative predictive value are calculated for PCT, CRP and WBC count taking blood culture as gold standard test. The sensitivity, specificity, positive predictive value and negative predictive value for procalcitonin were 92.59%, 56.52%, 71.4% and 86.6% respectively. The sensitivity, specificity, positive predictive value and negative predictive value for CRP were 55.55%, 56.52%, 60% and 52% respectively. The Sensitivity, specificity, positive predictive value and negative predictive value for WBC count were 40.74%, 52.17%, 50% and 42.85%.

Procalcitonin had highest sensitivity (92.59%) compared to that of CRP (55.55%) and WBC count (40.74%). The specificity of procalcitonin (56.52%) was almost same as that of CRP, but greater than the specificity of WBC count (52.17%) and lesser than that of platelet count (86.95%). The positive predictive value (71.4%) and negative predictive value (86.6%) of procalcitonin were higher than positive and negative predictive value of CRP and WBC count, which were (60%, 52%) and (50% and 42.85%) respectively.

When comparing procalcitonin with combine effectiveness of CRP, WBC count and platelet count, PCT had higher sensitivity (92.59%) and specificity(56.52%) than combined CRP,WBC and Platelet, which were 81.48% and 39.13%.

Platelet count was reduced (<1 lakh) in 13 neonates out of 50 neonates. The sensitivity, specificity, positive predictive value and negative predictive value of platelet count were 37.03%, 86.95%, 76.92% and 54.05% respectively. Platelet count had high specificity (86.95%) compared to other tests.

Combination of PCT and CRP had 100% sensitivity but at the cost of specificity (34.78%), where as the combination of PCT and platelet had both high sensitivity and specificity which were 96.29% and 95.65% respectively.

Comparison of efficacy of procalcitonin, CRP and WBC count by ROC curve analysis showed significant difference between the efficacy of procalcitonin and CRP with p value of 0.046 (<0.05), and between procalcitonin and WBC count with p value of 0.0315. The difference between the efficacy of CRP and WBC count was not significant p= 0.916 (p> 0.05).

When both culture positive and culture negative sepsis group were included in the analysis, the specificity of procalcitonin (87.5%), CRP (75%) and WBC count (62.5%) were increased.

The association between sample interval (duration between onset of symptoms and blood sampling) with CRP and PCT levels by partial correlation showed there was strong association between sampling interval and CRP level, with Pearson's correlation $r=0.86$ and $p<0.05$. Sampling interval more than 10 hours was associated with increased positivity of CRP. Whereas the correlation between sampling interval and procalcitonin was not significant $p>0.05$. Procalcitonin was positive at short sampling interval as earlier as 1 hour.

In our study procalcitonin value of ≥ 2ng/dl has sensitivity & specificity of 92.59% and 56.52%. This is similar to the study conducted by **Boo N Y et al**[47] on procalcitonin which showed sensitivity of 88.9% and specificity of 65.2%.

The positive predictive value and negative predictive value of procalcitonin in our study was 71.4% and 86.6% respectively. Similar study conducted by **Ibeh Isaiah et al**[52] had showed procalcitonin with positive predictive value and negative predictive value 92.6% and 80% respectively.

In our study CRP level ≥ 1mg/dl has sensitivity 55.55% and specificity 56.52%. This is comparable to the study conducted by **Boo N Y et al**[47] which showed sensitivity and specificity of CRP were 55.6% and 89.9% respectively.

The sensitivity, specificity, positive predictive value and negative predictive value of WBC count (<5000 or > 20,000) in predicting neonatal sepsis were 40.74%, 52.17%, 50% and 42.85% respectively. Similar study conducted by **Mohammad Ibrahim Aboud et al**[60] showed the sensitivity, specificity, positive predictive value and negative predictive value of WBC count were 72%, 63%, 66% and 69% respectively ,while that of CRP (> 2mg/dl) were 80%, 77%, 77% and 90% respectively and that of procalcitonin (> 0.8ng/dl) were 84%, 86%, 86% and 84% respectively.

In this study out of 27 positive blood culture, 17 (62.9%) were positive for Klebsiella pneumonia followed by Coagulase negative staphylococcus which was positive in 4 cases (14.8%). This was comparable to the study conducted by **Kurien Anil Kuruvilla et al**[58] in Tamilnadu, where they showed most common organism causing early onset sepsis was E.coli and late onset sepsis was Klebsiella pneumoniae.

In our study out of 27 culture positive cases thrombocytopenia was present in 13 cases (48%) which was comparable to the study conducted by **Abdallah Alshorman et al[59].** The study showed thrombocytopenia was present in 42.8% of culture positive sepsis.

SUMMARY

1. Number of cases studied : 50
2. Male =26 and female = 24
3. Age : >72 hrs -27, < 72hrs -23
4. Gestational age distribution

Table:19

≥ 37 weeks	34
34-36 weeks	5
32-34 weeks	3
30-32 weeks	1
28-30weeks	2

5. Weight distribution

Table:20

< 1 kg	2
1- 1.9 kg	14
2- 2.9 kg	21
3- 3.9 kg	11
>4kg	2

6. Number of culture positive cases : 27

7. Number of early onset sepsis among culture positive :14

8. Number of late onset sepsis among culture positive : 13

9. Frequency of organisms

Table:21

Klebsiella pneumoniae	17
Coagulase negative staphylococcus	4
Enterobacter spp	3
Pseudomonas aeruginosa	2
Enterococcus	1

10. Number of procalcitonin positive cases :35

11. Number of CRP positive cases :25

12. Number of WBC count positive cases : 22

13. Culture positive was taken as gold standard and diagnostic efficacy was calculated using 2×2 stastistic table

Table:22

Tests	Sensitivity	Specificity	PPV	NPV
Procalcitonin	**92.59%**	56.52%	71.4%	86.6%
CRP	55.55%	56.52%	60%	52%
WBC count	40.74%	52.17%	50%	42.85%
PLT	37.03%	**86.95%**	76.92%	54.05%
PCT/CRP	**100%**	**34.78%**	**64.28%**	**100%**
PCT/WBC	92.59%	34.78%	62.5%	80%
PCT/PLT	**96.29%**	**95.65%**	**96.29%**	**96.25%**
PCT/CRP/WBC/PLT	100%	26.08%	61.36%	100%
CRP/WBC	77.77%	43.37%	61.76%	62.5%
CRP/WBC/PLT	81.48%	39.13%	61.11%	64.29%

CONCLUSION

- Procalcitonin can be used as an early and reliable marker of neonatal sepsis.
- CRP and WBC count though can be used as initial sepsis screening; it cannot be substituted for procalcitonin.
- No combined investigation excluding procalcitonin was superior to procalcitonin.
- Combination of procalcitonin and CRP had highest sensitivity but low specificity.
- Combination of procalcitonin and platelet had both higher sensitivity and specificity.
- Sampling interval greatly influence the level of CRP but not procalcitonin level.
- Klebsiella Pneumoniae is the most common organism causing both early onset and late onset sepsis in our institution.

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CONSENT FORM

Your child …….. is being asked to be a participant in the research study titled "PROCALCITONIN AS AN EARLY AND RELIABLE MARKER OF NEONATAL SEPSIS"" in CMC Hospital, Coimbatore, conducted by Dr.J.Fouziya parveen , Post Graduate Student, Department of Paediatrics, Coimbatore Medical College. Your child is eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

RESEARCH BEING DONE

To show procalcitonin is an early and reliable marker of neonatal sepsis

PURPOSE OF RESEARCH

To diagnose neonatal sepsis at the earliest and there by provide early intervention

PROCEDURE

3.5 ml of blood is drawn from infants with features suggestive of sepsis for procalcitonin, CRP,WBC count and blood culture.

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about your child or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups; however your child will not be identified.

Statement of Consent

I volunteer and consent my child to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

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Signature /Left thumb impression of parent Date

PROFORMA

New born

- Name
- Age
- Sex
- Date of birth & time of birth
- Mode of delivery
- LSCS→ indication
- APGAR
- Birth wt

MOTHER

- Name
- Age
- Parity
- LMP/EDD
- Blood grouping & typing
- Duration of 2nd stage of labour
- H/O perinatal fever, foul smelling liquor

H/O bad CRP

H/OFeeding intolerance

Lethargy

respiratory distress

Seizure

Abdominal distension

jaundice

Examination

- Cry & activity :
- Colour
- Temperature
- Tone
- HR
- RR
- SPO2
- CVS
- RS
- ABDOMEN
- CNS

TIME GAP BETWEEN SYMPTOMS & SAMPLING:

LAB DATA

- WBC
- PCT
- CRP
- Other positive lab findings

MASTER CHART

S.NO	NAME	GEST AGE WEEKS	AGE HRS	SEX	WT KG	SYMPTOMS	SAMP INTVL HRS	PCT NG/DL	CRP MG/DL	WBC /CUMM	PLT L/CUMM	CXR	CSF		OTHERS	BLOOD CULTURE
													CELLS/DL	PROTEIN MG/DL		
1	B/O NAGAJOTHI	≥ 37	96	F	3	LETHARGY,ROF	12	28.91	7.9	3200	0.17	-	-	-	-	K. PNEUMONEA
2	B/O SEVI	≥37	96	M	1.8	LETHARGY,ROF	10	200	10.8	31000	0.15	-	-	-	-	K. PNEUMONEA
3	B/O VICTORIA	30-32	14	F	0.9	PPROM >96HRS	14	10.9	0.3	2500	1.8	-	-	-	-	K. PNEUMONEA
4	B/O DEVI	≥37	96	M	2.1	SEIZURE	8	7.3	0.2	15000	2.6	-	60	260	-	CONS
5	B/O SANGEETHA	34-36	72	M	1.8	LETHARGY,ROF,SKIN MOTTLING	4	7.6	0.4	14800	3.2	-	-	-	-	PSEUDOMONAS
6	B/O KAVITHA	28-30	1	F	1	PPROM >60HRS	2	6.8	0.51	17000	2.3	-	-	-	-	K. PNEUMONEA
7	B/O CHITRA	≥37	168	F	2.6	LETHARGY,ROF	12	0.09	4.1	12700	1.9	-	-	-	-	K. PNEUMONEA
8	B/O RADHAMANI	≥37	96	F	2.7	ROF, SEIZURE	18	2.59	2.1	15600	3.4	-	-	-	-	K. PNEUMONEA
9	B/O SUMATHI	≥37	120	M	2.8	ROF, SEIZURE	6	17.8	0.52	4500	5.8	-	120	370	-	K. PNEUMONEA
10	B/O MYELATHAL	≥37	72	M	1.8	LETHARGY,ROF	12	2.6	3.8	17600	0.84	-	-	-	-	ENTEROBACTER
11	B/O VIJI	34-36	120	F	1.6	ABDOMEN DISTENSION,ALTERED VOMITUS,LETHARGY	10	24.6	3.4	7200	0.47	-	-	-	-	K. PNEUMONEA
12	B/O SAGUNTHALA	≥37	72	F	2.2	LETHARGY,ROF	7	54	7.9	14800	1.68	-	-	-	-	PSEUDOMONAS
13	B/O SUMATHI	≥37	120	F	2.8	LETHARGY,ROF	22	3.7	0.4	4500	2.62	-	-	-	-	K. PNEUMONEA
14	B/O SINDU	34-36	192	F	1.7	LETHARGY,ROF	6	21.5	0.5	3500	0.81	-	-	-	-	K. PNEUMONEA
15	B/O JEYANTHI	32-34	360	M	1.5	RDS,ROF	7	3.8	8.2	7900	3.20	PNEUMONIA	-	-	-	CONS
16	B/O MALATHI	34-36	1	F	2.1	PROM 4DAYS,FOUL SMELLING LIQOR	1	17.3	0.4	9200	2.6	-	-	-	-	K. PNEUMONEA
17	B/O RADHA	≥37	72	M	1.9	ROF,FEVER	12	8.2	10.02	11600	0.21	-	-	-	-	K. PNEUMONEA
18	B/O GAYATHRI	≥37	408	F	3.3	RDS, ROF, FEVER	18	5.8	4.9	31700	3.93	PNEUMONIA	-	-	-	ENTEROBACTER
19	B/O VINODHINI	≥37	18	M	2.9	PROM >48 HRS,RDS	18	4.9	3.3	15000	4.12	-	-	-	-	ENTERCOCCUS
20	B/O ANNALAKSHMI	32-34	1	M	1.4	PPROM >24HRS	1	6.8	0.4	6800	0.3	-	-	-	-	K. PNEUMONEA
21	B/O INDRANI	28-30	6	F	0.9	PPROM >24HRS	6	5.9	0.3	2500	0.07	-	-	-	-	ENTEROBACTER
22	B/O KALPANA	34-36	72	M	1.7	RDS, SEIZURE	6	46.2	12.5	14000	1.64	-	-	-	-	CONS
23	B/O POORNIMA	≥37	2	M	2.6	PROM > 48HRS	2	3.2	0.09	17500	2.22	-	-	-	-	K. PNEUMONEA
24	B/O UMADEVI	≥37	72	F	3	LETHARGY,ROF	12	0.8	4	6000	0.53	-	-	-	-	K. PNEUMONEA
25	B/O LEELAVATHI	≥37	480	M	4	RDS, ROF	6	2.3	0.7	26000	1.95	PNEUMONIA	-	-	-	K. PNEUMONEA

S.NO	NAME	GEST AGE	AGE	SEX	WT KG	SYMPTOMS	SAMP INTVL	PCT NG/DL	CRP MG/DL	WBC /CUMM	PLT L/CUMM	CXR	CSF		OTHERS	BLOOD CULTURE
													CELLS/DL	PROTEIN MG/DL		
26	B/O SUDHA	≥37	168	M	1.9	LETHARGY, SEIZURE	18	2.7	9.4	3200	0.08	-	80	220	-	CONS
27	B/O KALAIVANI	≥37	216	F	2.6	RDS, ROF	12	17	8.9	24000	2.90	-	-	-	-	K. PNEUMONEA
28	B/O SATHYAPRIYA	≥37	144	M	3	LETHARGY,ROF	13	7.56	10.5	1300	0.64	-	500	H.V	-	-
29	B/O HEMALATHA	≥37	168	F	2.8	RDS	24	1.07	5.5	23000	1.83	PNEUMONIA	-	-	-	-
30	B/O DEVASHREE	≥37	480	M	3.2	RDS, ROF	18	1.7	10.28	26000	3.86	PNEUMONIA	-	-	-	-
31	B/O JULIANACRISTI	≥37	96	M	2.3	RDS, ROF	12	2.9	0.42	15300	0.82	PNEUMONIA	-	-	-	-
32	B/O PALANIAMMAL	≥37	144	M	3	ROF, SEIZURE	7	0.3	0.4	4300	2.16	-	420	H.V	-	-
33	B/O RASIDABEGUM	≥37	72	M	3	LETHARGY, SEIZURE	6	15.2	0.32	16300	2.75	-	60	185	-	-
34	B/O KAVITHA	≥37	312	F	4	RDS, FEVER	24	13.2	4.8	50000	1.62	PNEUMONIA	-	-	CT THORAX-CONSOLIDATION	-
35	B/O SUDHA	≥37	72	M	2.2	FEVER,ROF,RT KNEE SWELLING	12	0.8	10.28	10000	1.92	-	-	-	USG-JT EFFUSION 3ML PUS ASP	-
36	B/O DEEPA	≥37	42	M	3.2	ROF,LETHARGY, SEIZURE	4	4.2	0.06	11700	2.31	-	80	225	-	-
37	ROHITH	≥37	504	M	2	RDS,LOOSE STOOLS	28	57.9	3.8	29700	2.61	PNEUMONIA	-	-	-	-
38	B/O CHITRA	≥37	72	F	2.4	RDS	6	7.2	0.5	9700	1.75	PNEUMONIA	-	-	-	-
39	B/O KRISHNAVENI	≥37	46	M	3.2	RDS	5	4.8	0.6	26000	3.12	PNEUMONIA	-	-	-	-
40	B/O SUGANYA	≥37	360	M	2.8	RDS, ROF	18	0.3	0.32	6900	1.91	PNEUMONIA	-	-	-	-
41	B/O VAIRAPRIYA	≥37	384	F	3	LETHARGY,ROF, RDS	18	0.8	3.2	6800	3.32	PNEUMONIA	-	-	-	-
42	B/O BANUMATHI	≥37	552	M	2.1	LETHARGY,ROF, SEIZURE	16	2.37	6.3	3200	4.20	-	200	H.V	-	-
43	B/O MADHUMATHI	≥37	120	F	2.5	LETHARGY,ROF	10	1.85	4.7	23000	0.62	-	-	-	-	-
44	B/O PARAMESWARI	≥37	38	F	2	LETHARGY,ROF	8	1.47	0.5	8300	2.80	-	-	-	-	-
45	B/O TULASIMANI	≥37	72	F	3.8	ROF, ABDOMEN DISTENSION	6	9.2	3.8	27000	0.27	-	-	-	-	-
46	B/O CHANDRADEVI	≥37	72	M	1.9	ROF, ABDOMEN DISTENSION	12	1.3	0.4	4100	2.36	-	-	-	-	-
47	B/O SITAARA	32-34	1	M	1.3	PROM >48HRS	1	0.9	0.5	13000	2.58	-	-	-	-	-
48	B/O PUNITHA	≥37	120	F	2.6	ROF, ABDOMEN DISTENSION	12	1.9	0.3	12000	3.42	-	-	-	-	-
49	B/O PODUMPONU	≥37	144	F	1.9	LETHARGY,ROF	18	0.8	0.7	6000	5.26	-	-	-	-	-
50	B/O SANGEETHA	≥37	36	F	2.3	SKIN MOTTLING	8	0.37	0.4	6000	1.24	-	-	-	-	-

ABSTRACT

OBJECTIVE: To determine usefulness of procalcitonin as an early and reliable marker of sepsis and to compare its efficacy with C-reactive protein and WBC count in predicting neonatal sepsis.

METHOD: A total of 50 neonates with features or risks of sepsis were included in the study. Blood samples were drawn for procalcitonin, CRP, WBC count and blood culture before starting antibiotics. Neonates were divided into three groups based on blood culture and other investigations like CSF analysis, chest x-ray, as culture positive sepsis (27), culture negative sepsis (15), and suspected sepsis (23). The diagnostic value of procalcitonin was calculated using blood culture as gold standard investigation and compared with diagnostic value of CRP and WBC count.

RESULTS: Serum levels of PCT were significantly higher in culture positive group. The sensitivity, specificity, positive predictive value and negative predictive value of PCT were 92.59%, 56.52%, 71.4% and 86.6% respectively. The sensitivity, specificity, positive predictive value and negative predictive value for CRP were 55.55%, 56.52%, 60% and 52% respectively. The Sensitivity, specificity, positive predictive value and negative predictive value for WBC count were 40.74%, 52.17%, 50% and 42.85% respectively.

CONCLUSION: Procalcitonin can be used as an early and reliable marker of neonatal sepsis. CRP and WBC count though can be used as initial sepsis screening; they cannot be substituted for procalcitonin. No combined investigation excluding procalcitonin was superior to procalcitonin.