"EFFECTIVENESS OF SERUM PROCALCITONIN AND SERIAL LEVELS OF C-REACTIVE PROTEIN VERSUS BLOOD CULTURE IN EARLY DIAGNOSIS OF NEONATAL SEPSIS."

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This is to certify that the dissertation entitled **"EFFECTIVENESS OF SERUM PROCALCITONIN AND SERIAL LEVELS OF C-REACTIVE PROTEIN VERSUS BLOOD CULTURE IN EARLY DIAGNOSIS OF NEONATAL SEPSIS"** is a bonafide research work done by ***REG NO: BI0116004.***

Dr. Sumati A. Hogade **MD.**
Professor & Head,
Department of Microbiology,
J. N. Medical College,
Belagavi – 590010

Date:
Place: **Belagavi**

Dr. N. S. Mahantashetti **MD.(Paed)**
Principal,
J. N. Medical College,
Belagavi – 590010

Date:
Place: **Belagavi**

LIST OF ABBREVIATIONS

- EOS- Early Onset Sepsis
- LOS-Late Onset Sepsis
- PROM-Premature Rupture Of Membranes
- UTI-Urinary Tract Infection
- WHO-World Health Organisation.
- CRP-C-Reactive Protein
- PCT-Procalcitonin
- TNF-Tumour Necrosis Factor
- WBC-White Blood Cells
- LSCS-Lower Segment Ceaserian Section
- NVD-Normal Vaginal Delivery
- LBW-Low Birth Weight
- ESR-Erithrocyte Sedimantation Rate
- IUGR-Intra Uterine Growth Retardation
- POG-Period Of Gestation
- GCSF-Granulocyte Colony Stimulating Factor

ABSTRACT

INTRODUCTION:

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Rapid and accurate diagnosis of neonatal sepsis is often Cumbersome in routine clinical practice because of its non specific clinical presentation.

Although Blood culture is warranted as gold standard there is a substantial time delay as the blood culture result is ready only after 24 to 72 hours. Therefore, using rapid diagnostic methods including laboratory markers could be beneficial for the diagnosis of neonatal sepsis.

AIM AND OBJECTIVES:

- To know the Effectiveness of serum Procalcitonin , C-Reactive Protein and heamatological parameters versus Blood culture in early diagnosis of Neonatal Sepsis in Neonatal Intensive Care Unit.

MATERIALS AND METHODS:

Study area: Neonatal intensive care unit at KLE's Dr. Prabhakar Kore Hospital, Belagavi.

Study design: A cross sectional study.

Study period: January 2017 to December 2017 over a period of 1 year.

Study participants: Neonates with signs suggestive of sepsis admitted to Neonatal intensive care unit at KLE's Dr. Prabhakar Kore Hospital,Belagavi.

Sample size: Sample size is calculated by using the formula :

$$\frac{(Z\alpha)^2 \text{ x sensitivity x (100-sensitivity)}}{}$$

(relative error) ^{2} x prevalance

where, :

$Z\ \alpha$ (constant) = $1.96 \cong 2$

S = Sensitivity = 81

d = relative error = 5%

p = prevalence = 7%

= $(2)^2$ x 81x(100-81)/$(5)^2$ x7

= 4x81x19/25x7

= 6156/175

= $35.17 \cong 36$.

Sample size:36.

Sampling procedure: Universal sampling method.

Inclusion criteria:

Neonates who are going to be started on antibiotics with :

a) **Neonatal risk factors like** Low birth weight, Preterm, Prematurity or Twins presenting with any of the following clinical signs:

- Convulsions
- Respiratory rate >60 breaths/min .
- Severe chest indrawing .
- Nasal flaring.
- Grunting .
- Buldging /depressed fontanelle.
- Discharge draining from the ear.
- Redness around umbilicus extending to the skin.
- Temperature .37.7˚C (or feels hot) or ,35.5˚C(or feels cold).

- Lethargic or unconscious(not aroused by minimal stimulus).
- Reduced movements.
- Not able to feed (not able to sustain suck).
- Not attaching to the breast.
- No suckling at all.
- Crepitations.
- Cyanosis and
- Reduced digital capillary refill time.

Any of the signs listed above implies high suspicion of serious bacterial infection.

OR WITH

b) Maternal risk factors :

- Premature rupture of membranes.
- Prolonged labour(sum of 1^{st} and 2^{nd} stage of labour is >24 hours).
- Rupture of membranes(>24 hours).
- Maternal fever with evidence of bacterial infection within two weeks prior to delivery.
- Foul smelling or meconium stained liquor.
- Urinary tract infection.
- Caesarean section.
- Single unclean or more than 3 sterile vaginal examinations.
- Twin pregnancy.
- Invitro conception.
- Preclaamsia.
- Gestational diabetes mellitus.
- Cervical stitch insitu.

Exclusion criteria:

a) Neonates who had Birth asphyxia, Aspiration syndrome.

b) Laboratory findings which are suggestive of Inborn errors of metabolism

c) Neonates with Congenital anamolies .

d) Referred cases already treated with antibiotics.

Methodology:

- Written consent was taken from the Mother.
- 1-2ml of venous blood was collected following aseptic precautions by a trained staff prior to the administration of antibiotics for the sepsis screening, which included Blood culture, Haematological parameters, serum Procalcitonin level and serum C-Reactive Protein level.A Second Blood sample of was collecte to determine the serial levels of C-Reactive Protein which is done 72 hours apart after the administration of Antibiotics.
- The Sepsis work up included:
    a) Haematological parameters.
    b) Blood culture to isolate the organism.
    c) Serum Procalcitonin Level: By Quantitative method using B.R.A.H.M.S PCT kit using cobas e analysers.
    d) Serum CRP levels :By Latex Serology test using Cobas c analysers.

Statistical Analysis: To evaluate the Effectiveness of serum Procalcotonin levels and serial levels of serum C-Reactive Protein against Blood culture and Haematological parameters, Sensitivity analysis was done. Indices like Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value was competed for each of the screening procedures.

RESULTS:

The screening tests applied in the present study showed the following results:

a) PCT: Sensitivity-65.59%

Specificity-53.84%

Positive Predictive Value-72.72%

Negative Predictive Value-50%

b) 1^{ST} CRP: Sensitivity-50%

Specificity-92.30%

Positive Predictive Value-92.30%

Negative Predictive Value-52.17%

c) Haemoglobin percentage: Sensitivity-26.06%

Specificity-84.16%

Positive Predictive Value75%

Negative Predictive Value-39.28%

d) Total WBC counts : Sensitivity-61.11%

Specificity-53.84%

Positive Predictive Value-64.70%

Negative Predictive Value- 36.84%

e) Platelet counts : Sensitivity-47.05%

Specificity-69.25%

Positive Predictive Value-66.66%

Negative Predictive Value-37.5%

CONCLUSION:

PCT showed the highest sensitivity followed by total WBC counts and CRP.CRP showed highest specificity and positive predictive value among all other

markers. But neither of these markers are 100% sensitive nor 100% specific to be relied as a sole marker. We would like to conclude that blood culture even though considered as gold standard it is time consuming and at times gives false negative results. The greatest predictability can be achieved by the combination of total WBC counts, CRP and PCT rather than a single biomarker. So it is high time to initiate rigorous steps to expand the continuing search for a definitive diagnostic biomarker using multi-centric studies based on a harmonized protocol.

Key words: Neonatal septicaemia, Procalcitonin,C-Reactive Protein, Blood culture

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INTRODUCTION

DEFINITION:

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life.[(1)]

It comprises of various systemic infections like Septicemia, Pneumonia, Meningitis, Arthritis, Osteomyelitis and Urinary tract infections. Superficial infections like Oral trush, Conjunctivitis are not included under neonatal sepsis .

Neonatal septicemia continues to be one of the leading causes of neonatal morbidity and mortality worldwide. The incidence varies from country to country , but is much higher in developing countries. WHO estimates, there are about 5 million neonatal deaths a year, 98% occurring in developing countries. In developing countries, neonatal mortality (i.e deaths in the first 28 days of life per 1000 livebirths) from all the causes is about 34. Most of these deaths occur in the first week of life, of which most on the first day[(2)].

TYPES OF NEONATAL SEPSIS:

Neonatal sepsis is divided into two categories depending on the Onset as:

a) **EARLY ONSET SEPSIS (EOS)**- which occurs within 72 hours of life. Neonates with early onset sepsis present usually with Respiratory distress and Pneumonia. The source of infection here generally is Maternal genital tract. In case of severe sepsis, the neonate may be symptomatic at birth. The usual presentation in EOS is with respiratory distress and pneumonia. Few maternal/ perinatal conditions have been found to be associated with an increased risk of

EOS. Appropriate recognition of these potential risk factors would aid in diagnosing sepsis early.

From the studies done by Narang and Bhakoo[3] from India, the following risk factors appear to be associated with an increased risk of early onset sepsis:

1. **Low birth weight (<2500 grams) or prematurity**
2. **Febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery**.
3. **Foul smelling and/or meconium stained liquor**.
4. **Prolonged rupture of membranes (PROM).**
5. **Single unclean or > 3 sterile vaginal examination(s) during labor.**
6. **Prolonged labor (sum of 1st and 2nd stage of labor > 24 hours)**
7. **Perinatal asphyxia (Apgar score <4 at 1 minute).**

b) LATE ONSET SEPSIS (LOS)- which occurs after 72 hours of life. Neonates usually present with Septicemia,Meningitis and Pneumonia. In LOS ,the source of infection usually is either nosocomial (hospital-acquired) or community-acquired and neonates present with septicemia, pneumonia or meningitis. The factors which predispose to nosocomial sepsis include low birth weight, prematurity, admission in intensive care unit, mechanical ventilation, undergoing invasive procedures, administration of parenteral fluids[4].

Factors that predispose to the community-acquired LOS include poor personal hygiene, poor cord care, bottle-feeding, and pre lacteal feeds. In contrast, breastfeeding helps in prevention of infections.

CLINICAL CRITERIA FOR DIAGNOSIS OF NEONATAL SEPSIS[2] [4]:

Neonates with risk factors like Low birth weight, Preterm, Prematurity or Twins presenting with any of the following clinical signs:

- Convulsions.
- Respiratory rate >60 breaths/min .
- Severe chest indrawing .
- Nasal flaring.
- Grunting .
- Buldging /depressed fontanelle.
- Discharge draining from the ear.
- Redness around umbilicus extending to the skin.
- Temperature .37.7˚C (or feels hot) or ,35.5˚C(or feels cold).
- Lethargic or unconscious(not aroused by minimal stimulus).
- Reduced movements.
- Not able to feed (not able to sustain suck).
- Not attaching to the breast.
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Any of the signs listed implies high suspicion of serious bacterial infection.

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Maternal risk factors:

- Premature rupture of membranes.
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- Maternal fever with evidence of bacterial infection within two weeks prior to delivery.
- Foul smelling or meconium stained liquor.
- Urinary tract infection.
- Caesarean section.
- Single unclean or more than 3 sterile vaginal examinations.
- Twin pregnancy.
- Invitro conception.
- Preclampsia.
- Gestational diabetes mellitus.
- Cervical stitch insitu.

Rapid and accurate diagnosis of neonatal sepsis is often Cumbersome. The clinical manifestations of neonatal sepsis overlaps with those of non-infectious conditions, such as the Meconium aspiration syndrome, Respiratory distress syndrome, and Hemodynamic instability of various underlying etiologies.

In general, the identification and treatment of newborns with infection is unsatisfactory in many developing country settings. Sick newborns present with nonspecific signs and symptoms, a clinical diagnosis of neonatal sepsis is difficult in routine clinical practice even in the most sophisticated settings[(5)].

Although Blood culture is warranted as gold standard and distinguish sepsis from non-infectious conditions, it lacks sensitivity and specificity as blood culture may yield false positive results because of contamination. Also it can remain negative despite generalized bacterial infection. There is a substantial time delay as the blood culture result is ready only after 24 to 72 hours[(1)] .Cases of suspected but culture-negative sepsis outnumber culture-positive ones by at least 15–20 times.

Infection markers evaluated in the neonatal intensive care unit that have been studied in Preterm or Term neonates are classified as:

- **Haematological markers.**
- **Acute phase proteins and other proteins.**
- **Components of the complement system.**
- **Chemokines,cytokines and adhesion molecules.**
- **Cell surface molecules**

Early diagnosis followed by appropriate treatment of all newborns with clinical suspicion of sepsis is an important strategy in preventing life threatening complications and death. In developing countries like India, use of rapid diagnostic tests such as Polymerase Chain Reaction(PCR) and Bacterial rapid antigen tests is too expensive to use for diagnosis of neonatal sepsis and where culture and sensitivity facilities are limited, so in majority of newborns; initial suspicion/diagnosis of neonatal sepsis is based on clinical features which are most of the times nonspecific, which results in initiation of empirical antibiotic treatment.

The present trend which is being applied for all the neonates who are suspected to have neonatal sepsis may lead to unnecessary and increased antibiotic consumption, a higher incidence of the side-effects due to their use,

increased resistance to the antibiotics, a long hospitalization, the separation of the neonates from their mothers and increased health costs.

Therefore, using rapid diagnostic methods including laboratory markers could be beneficial for the diagnosis of neonatal sepsis. Hence it's necessary to rely on early diagnostic markers. Out of the early diagnostic markers available, C-Reactive Protein and Procalcitonin has the highest sensitivity and specificity rates[6].

C- reactive protein (CRP) has been widely used as a diagnostic tool for identification infection. Although, a high level of CRP was shown to be a sensitive and classical marker of inflammation in several studies, but it cannot differentiate bacterial infections from other infections. Moreover, non-infectious conditions like Perinatal Asphyxia, Respiratory Distress Syndrome, Meconium Aspiration Syndrome and Post surgical period can induce abnormal values of CRP.

Procalcitonin (PCT) is an acute phase protein which has recently attracted attention as a measurable laboratory marker of sepsis. PCT increases during bacterial, fungal, and parasitic infections.

Localized bacterial infections, severe viral infections and inflammatory reactions of noninfectious origin do not or only slightly change the PCT level in contrast to CRP.

While some studies reported that PCT is more reliable than CRP for the diagnosis of neonatal sepsis, others did not find any advantage of PCT over CRP. There are several studies showing controversies on an ideal marker of sepsis[7]. As little information available based on comparison between these two potential markers, this present study was conducted.

AIM AND OBJECTIVES

This study was conducted with the following aim and objectives:

Aim:

- To know the Effectiveness of serum Procalcitonin , C-Reactive Protein and heamatological parameters versus Blood culture in early diagnosis of Neonatal Sepsis in Neonatal Intensive Care Unit.

Secondary objectives:

- To determine the prevalence of culture proven sepsis cases among the suspected cases of neonatal septicemia.
- To evaluate the distribution of neonatal septicemia cases according to the time of onset of sepsis.
- Gender wise distribution of sepsis.
- Distribution of sepsis according to gestational age.
- Distributional of sepsis according to birth weight.
- To assess maternal and fetal risk factors associated with neonatal sepsis.
- To study the bacteriological profile of neonatal septicemia.

REVIEW OF LITERATURE

EPIDEMIOLOGY:

Septicemia is one of the most commonly encountered problem in neonatal nurseries and contributes considerably in neonatal morbidity and mortality[8].Neonatal septicemia either acquired from the Mother (vertical transmission) or Nosocomial (horizontal transmission)is a formidable problem encountered in the neonatal unit and is the commonest primary cause of morbidity and mortality among neonates[9].

The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The NNPD network comprising of 18 tertiary care neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths[3].Three conditions: infection, birth asphyxia, and consequences of premature birth/low birth weight, are responsible for majority of these deaths.

Annually, 6.6 million under-five child deaths globally, in which about 44 percent occur during the first 28 days of life[10], this proportion is even higher – around 54 percent – in countries that belong to WHO South East Asia Region (SEAR).

In India, current NMR(SRS 2015) is 25 per 1,000 live births[11], about 69 percent of infant deaths and more than fifty percent of under-five child deaths in our country occur during the neonatal period .

The Early Neonatal Mortality Rate (ENMR) – that is deaths that occur during the first week of life - is 23 per 1,000 live births [(11)]. This implies that the early neonatal period alone accounts for about 45 percent of total under-five child deaths.

India contributes to one-fifth live births and more than a quarter of neonatal deaths that occur globally. About 0.76 million neonates died in 2012,which was the highest for any country in the world for that year[(11)]. A systematic analysis including the global, regional, and national causes of child mortality in 2012 prematurity and infections were identified to be the major causes of neonatal deaths in India [(12)].

A nationally representative survey on causes of child and neonatal mortality done by Awasthi et al which included data from the Million Death Study from India[(13)], found the significant causes for neonatal mortality being prematurity and perinatal asphyxia followed by sepsis. These findings go in hand with overall global pattern[(12).].

Every year an estimated 30 million newborns acquire infection and 1.2 million die of the disease[(14)].

A higher incidence of neontal sepsis is observed by many authors in developing countries than in developed countries. The reasons listed are high rate of home delivery in developing sepsis,often overseen by unskilled attendants ,unclean environment and limited resources[(15)(16)].

The incidence has been reported to vary between 1-10/1000 live births in developing countries and 1-4/1000 live births in developed countries[(8)].

Incidence is 7.1-38/1000 live births in Asia,6.25-23/1000 live birth in Africa, 3.5 –8.9/1000 live birth in south America and carribean ,6/1000 live births in USA and Australia[8].

Stoll et al[17] in his study reported the incidence of neonatal sepsis as:

India, Pakistan, Thailand, Malaysia	2.4-16/1000 live births.
Sub Saharan Africa	6-21/1000 live births.
Middle east and north Africa	1.8-12/1000 live births.

In India, literature indicates that the incidence varies from 11-24.5 /1000 live births in India[1].

Risk factors for Neonatal Septicemia:

The pathogenesis of neonatal septicemia are multifactorial. These factors interact together causing sepsis. They are as follows:

1. **Maternal/prenatal risk factors**
2. **Neonatal risk factors.**
3. **Nosocomial risk factors.**
4. **Others.**

1.Maternal or prenatal risk factors [18]:Mother can acquire infection during pregnancy or just before delivery and inturn transmit the infection transplacentally to the foetus.

A few maternal risk factors play a role in increased incidence of neonatal infections and they include:

a) **Prolonged Rupture Of Membranes (PROM)**: is defined as rupture of membranes prior to the onset of labor for more than 18 hours[13] . It's a major risk factor for chorioamnionitis and neonatal sepsis The risk of neonatal septicemia increases to approximately 10 fold in neonates born to mothers with rupture of membranes before delivery[19].

PROM was an important risk factor in early onset neonatal sepsis. A study done by kerur et al[20] showed that 90.2% of the mothers had PROM of more than 12 hours and 70.6% had PROM for 12-24 Hours.

b) **Chorioamniotis**: chorioamniotis is the inflammation of the placental membrane as a result of microbial invasion of amniotic fluid.It is usually associated with PROM and the risk of neonatal septicemia is increased by approximately 2-3 times in the presence of chorioamniotis and PROM.

Chorioamniotis appears to be an important febrile illness in the mother during pregnancy and during delivery.Attack rates of neonatal infection increase significantly in presence of chorioamniotis, diagnosed by amniotic fluid analysis or histologically. Clinically, signs of chorioamniotis include intrapartum fever ,maternal leucocytosis and uterine terderness.

A study conducted by Sawhney et al[21] showed that the newborn was at risk of acquiring infection when the gestational age was <34 weeks and when prolonged rupture of membranes for >24 hours was associated with amniotic fluid infection.

c) Foul smelling liquor:The presence of foul smelling liquor has been considered as an indication of chorioamniotis.Breakdown products of bacterial metabolism are thought to impart foul smell to the amniotic fluid.

Takkar et al[22] observed that the presence of foul smelling liquor was associated with 10% incidence of septicemia in their study.

d) Single unclean or more than 3 clean vaginal examination:

Schrag et al[13] reported that>2 vaginal examinations remained significantly associated with early onset sepsis with p value of 0.0005 and odds ratio of 1.1, 1.3 and 1.9 for 2-3,4 and ≥4 vaginal examinations respectively.

In our country, a lot of obstetrics practice is in the hands of untrained traditional birth attendants(dais).This leads to poor standard of asepsis in feild practice which includes conducting vaginal examination with ungloved hands [23-24].History of unclean vaginal examination are often associated with 10% deep infections[22]. Unclean vaginal examination was seen to be an independent factor in causing sepsis[8].

Singh et al[3] consider Vaginal examination performed without gloves ,with unsterile gloves ,any vaginal examination performed by an untrained birth attendant are at the high risk of sepsis.

e) Prolonged labour(sum of 1st and 2nd stage of labor > 24 hours) :

labour lasting more than 24 hours with prolonged duration of second stage of labour with rupture of membranes, increases the chances of invasion of microorganisms into the fetus[3].

f) Pre-eclampsia: About 40-50% of newborns ,whose mothers have pre-eclampsia have neutropenia that generally resolves after 3 days of age,these infants may be at increased risk of neonatal infection[25].

g) Maternal pyrexia: Maternal fever in association with polymorphonuclear leucocytosis and bacteriological evidence of infection has been investigated as a predisposing factor for neonatal sepsis[26].

Significant association was found with maternal pyrexia and neonatal septicemia in a study conducted by Movahedian et al[27].However in a similar study, Chacko et al[28]observed no association between peripartum fever in the mother and increased sepsis in the newborn.

h) Maternal UTI: unless treated and resolved before labour ,maternal UTI was associated with an increased risk of infection in the neonates ,presumably by increasing the risk of preterm birth and increasing the rate of chorioamniotis[29].

i) Maternal colonization with Group B Streptococcus(GBS) :Maternal colonization without clinical complications carries a 0.5-5% risk of early onset neonatal septicemia ,similar to the risk of uncomplicated PROM.

Gottof's comprehensive studies have identified the high risk of situations that increase the likelihood of neonatal GBS disease whom mother is colonized[30]. They are:

1. PROM>18 hours(risk increased 7 fold)
2. Maternal fever (risk increased 4 fold)
3. Prematurity (risk increased 7 fold).

j) Mode of presentation, Type and Place of delivery:

Higher rates of perinatal death due to infection, birth asphyxia and other causes is known with abnormal presentation, difficult labour and instrumental vaginal delivery[30].

Vaginal delivery may result in the colonization of microorganisms from the vaginal flora on the neonatal skin and gastrointestinal tract. Higher incidence of septicemia is also noted in neonates delivered at home or at tertiary hospital. Unclean delivery practices in home deliveries and prolonged hospital stay in neonates delivered by operative means at the hospital predispose them to infections acquired from the environment[31].

2.Neonatal factors:

Important predisposing factors for neonatal septicemia include Prematurity, Low Birth Weight, male sex, twins, certain congenital anamolies, birth asphyxia, difficult resuscitation and skin wounds.

a) Prematurity: Prematurity is the single most significant factor in neonatal septicemia,premature neonates have a 3-20 fold high risk compared to term neonates.

Studies have found consistently increased incidence as well as mortality in prematures.

There are a number of possible explainations for increased incidence of infection in premature neonates. Inherent in the preterm neonates are deficiencies in most arms of immune system, including immunoglobulin production, complement opsonic functions and phagocytic capability.

b) **Low Birth Weight:** Babies less than 2.5kgs are more likely to develop septicemia due to inappropriate immunological response.They have low levels of various complement systems and poor mucosal defences. There is a clear inverse relationship between birth weight to the rate of neonatal infections ,mortality and gestational age.Birth weight <1000 grams increase the neonatal infection rate by 26 fold when compared to term babies[22].

c) Male gender: Male infants are 2-6 times more at risk of neonatal septicemia than females[32].This may be linked to the X- linked immune regulatory genes.

3.Nosocomial risk factors:

Includes prolonged length of hospital stay,degree of overcrowding in neonatal units,invasive procedures,lack of hand washing by hospital personnel and indiscriminate use of prophylactic antibiotics that later alter the indigenous flora of the neonate eliminating sensitive strains and leads to colonization and proliferation of more virulent drug resistant strains of microorganisms[33].

a) Procedures:

Endotracheal intubation,Assisted ventilation,Umbilical catheterization and Exchange transfusion, when carried out without due regard to asepsis, constitutes important portal for entry of microorganisms.

Catheter related sepsis is commonly encountered in the neonatal intensive care unit. Single lumen vascular catheters are commonly used for early access in sick neonates.These include umbilical catheters (arterial and venous),central venous cathters(percutaneously placed silicone and surgically placed broviac)and peripheral arterial catheters.

Incidence of all vascular associated sepsis has been reported to be around 3.5% in hospitalized neonates[32].

In a stud y of nosocomial sepsis in neonates with single lumen vascular catheters,Bhandari et al[34] found a prevalence of sepsis in 10.5% neonates who had an umbilical artery catheter and 13.1% sepsis in infants with umbilical vein catheters.

b) Nursery outbreak:

Spread of microorganisms to newborns occurs by droplets from respiratory tract of patients,nursery personnel or other neonates. Organism may be transferred from from one baby to another by hands of nursery personnel.The greatest hazard however is an open or draining lesion.Colonization of the neonates skin, umbilicus, nasopharynx, gastrointestinal tract by pathogenic bacteria or fungi is a common prerequisite for subsequent nosocomial infection.Antibiotics interfere with colonization by the normal flora and falicitate colonization by pathogens.

4.Others:

a) Geographic factors[15]: Bacterial etiology of neonatal septicemia varies from one hospital to another and from a community to another.

b) Socio-economic status and Parenteral literacy:

The most significant factors causing septicemia are low birth weight and prematurity and and inversely related socio-economic status.Babies of poor illiterate parents have high incidence of neonatal infection because they are usually of low birth weight,delivered before 37 weeks of gestation,suffer malnutrition and have poor prenatal care.Their immunological status is comparatively diminished.Most deliveries

in poor families are conducted at home under improper aseptic conditions,further there is a delay in appreciating illness and seeking treatment[35]

ETIOLOGY OF NEONATAL SEPSIS:

Neonatal sepsis is caused by Gram-positive and Gram-negative bacteria and yeast. Although in developed countries, Gram positive bacteria remain the major source of in infection, the developing countries, Gram negative organisms have been implicated as the most common causes[36].

The spectrum of organisms that causes neonatal sepsis changes over times and varies from region to region and country to country. This may be due to the changing pattern of antibiotic use and changes in lifestyle[15].

Periodic evaluation and recognition of organisms responsible for neonatal sepsis is essential for the appropriate management of neonates.

As already mentioned, pathogens often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram-negative organisms are more common and represented by Klebsiella, Escherichia coli, Pseudomonas, and Salmonella. Of the Gram-positive organisms, most commonly isolated are Staphylococcus aureus, CONS, Streptococcus pneumonia and Streptococcus pyogenes[37]. According to the National Neonatal-Perinatal database report, Klebsiella as the predominant (29%) pathogen[38][39][40], which match with reports from other countries studies [41][42].

In general, the common bacterial causes of early onset sepsis (EOS) include[43]:

a) Group B- Streptococcus
b) Escherichia coli
c) Streptococcus pneumonia
d) Viridans streptococci
e) Enterococci
f) Haemophilus influenza
g) Neisseria meningitides
h) Neisseria gonorrhoeae
i) Listeria monocytogenes etc.

Of these, Group B- streptococcus and Listeria monocytogenes are usually of maternal origin.

The common bacteria causing late onset sepsis include[43]:

a) Staphylococcus aureus
b) Coagulase negative Staphylococci
c) Enterococci
d) Citrobacter
e) Enterobacter
f) Klebsiella pneumonia
g) Salmonella

Coagulase negative Staphylococci and Staphylococcus aureus in case of Gram positive bacteria, Escherichia coli & Klebsiella are found in frequent association with first episode of LOS in infants of very low birth weight.

Agents that are implicated to cause nosocomial infection include CONS, Escherichia coli, Klebsiella pneumoniae, Salmonella, Enterobacter aerogenes, Pseudomonas, Serratia and Citrobacter.

Ziba mosaiebi et al [(27)] from Iran reported that the most common organism isolated from neonatal sepsis was Klebsiella followed by Staphylococcus aureus, E.coli, Pseudomonas, Acinetobacter. Klebsiella was the commonest organism causing Early Onset Sepsis while Staphylococcus aureus was the commonest isolate in Late Onset Sepsis.

In a study done by Rahman et al[(44)] reported that the most common organism isolated from sepsis in neonates was Escherichia coli followed by Staphylococcus , Pseudomonas and Klebsiella.

A study done by Shaw CK et al from Nepal in the year 2007 reported that Staphylococcus aureus was the most frequent organism followed by Klebsiella and E.coli in causing sepsis in neonates[(45)].

Shalini Tripathi et al [(46)]from India reported Klebsiella pneumoniae to be the commonest organism contributing 32.5% and S.aureus (13.6%) as the second common cause of sepsis in intramural neonates. In case of extra-mural admissions , sepsis accounts for 38 % of deaths where Klebsiella(27.5%) was the commonest followed by Staphyloccocus aureus(14.9%). Though the commonest isolates are the same, the mortality tends to be higher in extramural cases.

Zakariya et al[(47)] in the year 2010 from Pondicherry has reported that Klebsiella pneumoniae was the commonest organism causing sepsis inneonates especially in developing countries.

FUNGAL SEPSIS:

Neonatal sepsis although has classically been attributed to bacterial organisms, prevalence of fungal sepsis among the neonates is on a rise in the present era of antibiotics. The wide availability of over-the-counter antibiotics and inappropriate use of broad-spectrum antibiotics in the community may explain the above situation. Importance of Candida infection in nursery and intensive care units (ICUs) is increasingly being recognized. Candida species contributes to most fungal infections in neonates, around 9-13%; a much smaller number may be attributed to Malassezia, Zygomycetes or Aspergillus[35].

Fungal sepsis is an important problem in sick new born infants,with a mortality rate between 21%[48] and 76%[49].although less frequent than gram positive or gram negative infections ,invasive infections with fungal organisms,primarily Candida species,results in substantial morbidity and mortality[50-51].

Fungal sepsis should be suspected in the critically ill neonate with negative blood cultures.approximately 2.5% of all bloodstream infections in very low birth weight neonates are estimated due to fungal etiologies[52].

The other causes of neonatal sepsis include : Adeno virus, Cytomegalovirus , Enterovirus, Human Herpes viruses including HSV and VZV, HIV, Parvovirus, Rubella virus, Plasmodia, Toxoplasma gondii etc., Infection acquired by the neonates after discharge are usually community acquired.

NEONATAL IMMUNITY:

The immune system and its response differs in neonates from that of adults. Both qualitative and quantitative defects have been observed and demonstrated in term as well as preterm neonates.

Neutrophils or the polymorphonuclear cells play a vital role in effective killing of bacteria. In neonates there is reduced adhesion and adherence of these cells to the lining vascular endothelium which further decreases its migration into the tissues. Also these polymorphs show deficient chemotaxis (neutrophil migration) because of the reduced expression of β-2 integrins , selectins and cell membrane adhesion molecules. Neonatal polymorphic cells are less deformable than adults. This limits the phagocytic activity of the cells and efficient killing of bacteria is impaired further in sepsis. Easy depletion of neutrophil reserve due to reduced bone marrow response makes the neonate more susceptible to infection.

The neonatal macrophage and monocyte chemotaxis is impaired in early childhood as compared to adults. It includes the circulating monocytes as well as the macrophages in liver, spleen and lungs which are responsible for immune modulation. The chemotactic, bactericidal, cytokine producing and antigen presenting activity of the monocyte-macrophage system are less competent at birth.

Activation of T-cells in neonates results in ineffective production of cytokines which participates in the stimulation of B-cells and their further differentiation [(46)]. The neonates are deficient of memory T-cells as well. Subsequent exposure of the neonate to the antigenic stimuli increases the memory T-cells.

In neonates NK cells are seen in far fewer numbers in peripheral circulation which are functionally immature resulting in lower levels of interferon-γ synthesis on primary stimulation than the normal natural killer cells.

As far as the humoral immunity is concerned , the ability of the neonate to generate immunoglobulin for an antigenic stimulus is initially low at birth. But the magnitude of this response rises rapidly with increase in post-natal age. Newborns usually lack antibody mediated protection against Enterobacteriaceae especially Escherichia coli.

The neonate is able to synthesize IgM, IgG, IgE in utero. Large proportion of IgG in neonates is maternally acquired in the late gestationalperiod. Its specificity is determined by the mother's previous antigenic exposure and lower levels are found with increasing prematurity. This maternally derived antibody falls rapidly after birth. The neonate is not capable of secreting IgA till 2-5 weeks after birth and receives it from the mother during breast- feeding. In total, the response to the polysaccharide antigens is diminished.

The concentration of the components of complement system vary widely among the neonates though their synthesis starts in the early gestation.The deficiency of the complement system is more observed in the alternate pathway than in the classical pathway. Premature neonates have still lower levels of complement activity.

The terminal cytotoxic components in the complement system that are responsible for efficient killing of Gram negative bacteria are deficient in neonates. Complement system is mainly responsible for bactericidal activity against E.coli and act as opsonins along with the antibody in phagocytosis.Because of lower levels of

fibronectin which is involved in neutrophil adherence and opsonisation , neonates show reduced opsonic efficiency against E.coli, S.pneumoniae, Group B Streptococci etc.

The Neonatal immune system with the individual deficiencies of the components and interdependence of all these factors in order to evoke an immune response as a whole conspire to convert the situation to a great hazard on exposing the neonate to infectious threats.

Pathogenesis of sepsis:

The unique pathophysiology contributes to the clinical syndrome of neonatal sepsis. Neonates are less efficient in triggering response to infection due to their deficient immune status compared to adults. Conditions co-existing with sepsis renders the diagnosis a complex process as its manifestations vary in neonates.

The pathogenesis depends on the following factors:

- The time of exposure
- Status of the host immune system and its response
- Quantity of the inoculums
- Virulence of the infecting microorganisms
- Maturity of the neonate
- Underlying co -morbid conditions
- Procedures done invasively
- Genetic predisposition
- Presence of transplacental maternal antibodies.

Transplacental infections can occur at any stage of gestation and its presentation varies. The timing of the infection during gestation determines the outcome. The fetus is maintained optimally in a sterile environment before birth. The organisms causing sepsis ascend from the maternal genital tract either during the rupture of amniotic membrane or during the course of labour which results in infection.

Chorioamnionitis which is the intra- amniotic infection is a major risk factor for EOS. Here sepsis begins in utero when the foetus inhales or swallows the infected amniotic fluid. The neonate can present with the symptoms within hours or days of birth when the colonised skin or mucosa is compromised.

Pyati et al[(53)](1983) reported that the preterm neonates are exposed to Group-B Streptococci in utero while the term neonates are often exposed to the organisms while passing through the birth canal. After birth, the neonates may acquire infection from mother and family members, inanimate sources used for resuscitation or health personnel via direct contact.

Most meningitis cases are due to hematogenous dissemination and less often due to contiguous spread.Mechanisms for elimination of the organisms are activated when bacteria gain access into the blood stream of the neonate. Normally the bacteria are efficiently killed by the monocyte-macrophage system. However,sometimes it may develop systemic inflammatory response syndrome and progress into sepsis.

Current concepts in the pathophysiology of sepsis[(54)]:

The earlier belief that the bacteria and their components like endotoxins (lipo-polysaccharides) of Gram negative bacteria and lipo-teichoic acid of Gram positive bacteria were responsible for the direct toxic effects is now being co-added by other factors and modified.

Recent research indicated that the physiological effect generated by bacterial infections are largely mediated by proinflammatory cytokines activated in response to the presence of microbial components within the vascular compartment.The prominent among the cytokines are Tumour Necrosis Factor(TNF) and interleukin-1(IL-1) which are rapidly produced by macrophages,endothelial cells and many other cellular elements on exposure to bacterial products.these cytokines induce fever, acute phase changes, hypotension and endothelial injury, alterations which are similar to those observed after endotoxins or bacterial inoculation.a number of other mediators like interleukin-6(IL-6),Interleukin-8(IL-8),Platelet activating factor(PAF),Interferon-γ,microphage proteins,arachidonic acid metabolites and some still unidentified substance also amplify the systemic inflammatory response[(54)].

These components of complement C3a and C5a are capable of provoking release of histamine from mast cells and basophils,mediating contraction of smooth muscle and increased capillary permeability which can agrrevate hypotension in sepsis.

The intrinsic coagulation pathway may e activated by a direct interaction between endotoxins and coagulase factor XII .Endotixins can induce the release of the tissue necrosis factor by monocytes and endothelial cells directly or through

cytokines,thus factor VII and the extrinsic coagulation pathway is also activated,leading to the development of dessiminated intravascular coagulation .Factor XII also stimulates the conversion of prekallikrein to kallikrein and subsequent conversion of kininogen to bradykinin which is a potent vasodilator.

Neutrophils initiate phagocytosis and microbial killing by degranulation and release of several proteolytic enzymes and toxic oxygen radicals ,a process that can also cause damage to nearby tissues.additionally neutrophils induced damage to the surrounding contributes to the separation of tight endotheliai cell junctions of the capillaries and the development of vascular leakage and septic shock.

NEWER DIAGNOSTIC TESTS DIAGNOSIS OF NEONATAL SEPSIS [46]:

"Isolation of bacteria from blood is a standard and most specific method used to diagnose neonatal sepsis. Positive cultures ranged from 8% to 73% in the diagnosis of potential neonatal sepsis. An additional drawback of culture based diagnosis is the 24–48 hour assay time. Newer diagnostic tests can be grouped into:

1. **Acute phase reactants**
2. **Cell surface markers**
3. **Granulocyte colony stimulating factor**
4. **Cytokines**
5. **Molecular genetics**
6. **Mol cell proteomics**

1. **Acute phase reactants:**

These groups of endogenous peptides are produced by the liver as part of an immediate response to infection or tissue injury. These reactants are C- reactive

protein, Procalcitonin, Fibronectin, Haptoglobin, Lactoferrin, Neopterin and Oromucosoid.

C-reactive protein[55][56][57]:CRP is a rapidly responsive acute phase reactant,an abnormal β-globulin,synthesized in the liver within 6-8 hours of an inflammatory stimulus. CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage, with a half life of 19 hours and its level may rise to more than 1000 fold during an acute phase response.

CRP is a widely known marker commonly used for early detection of neonatal sepsis in nursery. There is reported wide variation in normal CRP level of newborns as its sensitivity & specificity as well as regarding its use as indicator of sepsis.

Moreover, CRP has been shown to be elevated not only in infectious but also in non-infectious conditions of neonates including Meconium aspiration, Respiratory distress syndrome, Fetal hypoxia and Intraventricular hemorrhage.

Different cut-off values for raised CRP have been recommended by different studies using varying protocols. Though several studies confirmed that CRP levels are useful in the early diagnosis of sepsis, there are reports to the contrary . The cascade of events in sepsis leading to rise of CRP may take few hours to days; therefore predictive value of CRP is higher after 24 to 48 hours of infection.

Procalcitonin [58][59][60][61][62]**:** Procalcitonin (PCT) is produced by Monocytes and Hepatocytes which begins to rise four hours after exposure to bacterial endotoxin, peaking at six to eight hours, and remaining raised for at least 24 hours with a half life of 25–30 hours. Several studies have shown that serum Procalcitonin concentrations increase appreciably in systemic bacterial infection.

Procalcitonin (PCT), a precursor of the hormone calcitonin, is another biomarker for bacterial infection. PCT is present at very low concentrations of 0.033 ng/ml in the serum of healthy individuals and is known to increase by up to 1000-fold under inflammatory conditions. It is reported to rise within 2–4 h of infection and peaks at 6–8 h. Persistent elevated levels are indicative of the persisting infection or sepsis.

As a biomarker for bacterial infection, most studies suggest PCT to be a useful and accurate biomarker and more useful than other common inflammatory markers. Also studies have reported significantly elevated levels of PCT in patients with sepsis compared with those without sepsis. Studies have also reported PCT being used as a prognostic marker, indicating that PCT levels are a good indicator of response to treatment, severity of sepsis.

Similar to CRP, it is unclear if PCT can be used to distinguish Gram-positive from Gram-negative bacterial infections, which are treated with different strategies. Studies showed PCT helps to distinguish fungal and viral infections from bacterial infections. During viral infections, PCT levels are reported to remain at low levels, often at concentrations found in healthy individuals.

Unlike other hematological indices, PCT has been reported to be useful in indicating the severity of infection, progress following the treatment, and predicting outcomes. However, false negative cases had been found and very high serum concentrations were detected in patients with respiratory distress syndrome, acute lung and inhalation injuries, hemodynamic failure, and severe trauma, even in the absence of bacterial infection.

In summary, PCT levels elevate during EOS and LOS and its overall diagnostic utility is comparable with CRP. However its use is limited in developing countries due to high cost.

2. Cell surface markers:

Neutrophil CD11b and CD64 appear to good markers for diagnosis of early and late onset infections. CD11b is a subunit of the b2 integrin adhesion molecule, normally expressed at a very low concentration on the surface of non-activated neutrophils. There is a 2–4 fold increase in neutrophil CD11b expression in infants with blood culture positive sepsis.

But in preterm infants with RDS, significant activation of circulating phagocytes occurs within 1 to 3 hours of the onset of mechanical ventilation, independent of surfactant administration, which indicates that mechanical ventilation may be the inducer of this systemic inflammatory response. Therefore, CD11b is not a good marker for neonatal sepsis.

3. Granulocyte colony stimulating factor:

Granulocyte colony stimulating factor (GCSF), a mediator produced by bone marrow, facilitates proliferation and differentiation of neutrophils, and has been proposed to be a reliable infection marker for early diagnosis of neonatal sepsis. A concentration ≥ 200 pg/ml has a high sensitivity (95%) and negative predictive value (99%) for predicting early onset neonatal bacterial and fungal infections.

4. Cytokines:

As antigen specific immunity develops later e.g. at 2 years of age in the case for encapsulated bacteria, neonates initially depend on natural (innate) immunity. This includes phagocytes (by monocytes, tissue macrophages, and neutrophils), natural killer cells, and humoral mediators (CRP, complements, and transplacentally acquired maternal antibodies).

Newborn infants display a higher percentage of IL6 and IL8 positive cells than do adults. There is sharp rise in IL6 concentration on exposure to bacterial products, which precedes the increase in CRP. Umbilical cord blood IL6 has consistently been shown to be a sensitive marker for diagnosing early onset neonatal sepsis at the onset of infection compared with other biochemical markers, including CRP, IL1ß, TNFα, and E- selectin, but sensitivity is reduced at 24 and 48 hours because IL6 concentrations fall rapidly and become undetectable after 24 hours.

Tumour Necrosis Factor α(TNFα) : is a proinflammatory cytokine that stimulates IL6 production and has a broad spectrum of biological actions on several types of target cell, both immune and non-immune. Newborns developing early onset infection are born with higher TNFα concentrations than non-infected infants.

Other markers studied over the last few years include adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1, E- selectin, L-selectin) and complement activation products (C3a-desArg, C3bBbP, sC5b-9), IL-1alpha, IL-1beta, IL receptor antagonist (IL1ra) which have been found to be significantly increased during sepsis, but require further evaluation for clinical application in the diagnosis of newborn infection.

5. Molecular genetics:

Polymerase chain reaction (PCR) analysis relies on the fact that the bacteria specific 16S rRNA gene is highly conserved in all bacterial genomes, is a useful method for identification of bacteria in clinical samples. Amplification targeting of this 16S rRNA gene is a potentially valuable clinical tool in samples with low copy numbers of bacterial DNA, as this gene is present at 1 to more than 10 copies in all bacterial genomes. The gene also has a number of divergent regions nested within it, so PCR can be targeted for species specific detection of bacteria in clinical samples. This technology has also been reported to be a very sensitive (100%) and rapid method for detecting potential pathogens in amniotic fluid commonly involved in the pathogenesis of preterm labour and adverse neonatal outcome.

However, the performance of broad range PCR analysis at a level of high analytical sensitivity is complex and remains one of the most challenging PCR applications in the diagnostic laboratory.

6. Role of Proteomics for diagnosis of neonatal infection:

It was found significant alterations in levels of eight serum proteins in infected preterm neonates (specifically P- and E-selectins, interleukin 2, soluble receptor α, interleukin 18, Neutrophil neutrophil elastase, urokinase plasminogen activator and its cognate receptor, and C-reactive protein) were observed at statistically significant increased levels.

Molecular tools (16S-rRNA) demonstrate that the diversity of microbial agents of intra-amniotic infection exceeds what is suspected clinically or is documented by cultures.The resulting inflammatory process has the potential to

damage the fetus in utero. Stepwise algorithms (mass restricted score) have been developed to extract proteomic profiles characteristic of amniotic fluid inflammation.

The mass restricted score includes four proteomic biomarkers: defensin-2, defensin-1, S100A12, and S100A8 proteins. Other amniotic fluid biomarkers relevant for preterm birth are S100A9 and insulin-like growth factor-binding protein 1. S100A12 - ligand for the receptor of advanced glycation end products - has the strongest association with histological chorioamnionitis and funisitis. So the conclusion was - Presence of S100A12 and S100A8 in amniotic fluid is predictive of early-onset neonatal sepsis and poor neurodevelopmental outcome.

Estimation of Total WBC Counts, Absolute Neutrophil Count and Micro ESR can be done. The value of Total Leucocyte Count in predicting sepsis is considered non-specific as it is normal in one-third of neonates showing culture positivity. So it cannot be taken as a sole reliable marker in diagnosing sepsis. Leucopenia is considered a fairly specific indicator in detecting sepsis than leukocytosis.

Among the neutrophil indices, Absolute Neutrophil Count (ANC) and Total Leucocyte Count showed the highest specificity and sensitivity which makes it a better marker when compared with other markers.

As a prognostic indicator platelet count has gained much less significance because of its limited predictive value. As a late event in bacterial infection nearly 50% of them develop thrombocytopenia making it a less reliable marker. It is also elevated in a number of disorders other than sepsis".

These Circulating and cell associated molecules i.e Total Leucocyte Count, Absolute Neutrophil Count, Ratio of Total & Immature Neutrophils, C-reactive protein , various cytokines including IL-6 &8 and TNF-α ,Procalcitonin are proposed as useful markers in diagnosing sepsis. But none of them are found to be 100% sensitive or specific.

MATERIAL AND METHODS:

Study area:

Neonatal intensive care unit at KLE's Dr. Prabhakar Kore Hospital,Belagavi.

Study design: A cross sectional study.

Study period: January 2017 to December 2017 over a period of 1 year.

Study participants: Neonates with signs suggestive of sepsis admitted to Neonatal intensive care unit at KLE's Dr. Prabhakar Kore Hospital, Belagavi.

Sample size: Sample size is calculated by using the formula :

$$\frac{(Z\alpha)^2 \times \text{sensitivity} \times (100-\text{sensitivity})}{(\text{relative error})^2 \times \text{prevalance}}$$

where, :

$Z\ \alpha$ (constant) = $1.96 \cong 2$

S = Sensitivity = 81

d = relative error = 5%

p = prevalence = 7%

$= (2)^2 \times 81 \times (100-81)/(5)^2 \times 7$

$= 4 \times 81 \times 19/25 \times 7$

$= 6156/175$

$= 35.17 \cong 36.$

Sample size: 36.

Sampling procedure: Universal sampling method.

Inclusion criteria[2][4]**:**

Neonates who are going to be started on antibiotics with :

a) **Neonatal risk factors like** Low birth weight, Preterm, Prematurity or Twins presenting with any of the following clinical signs:

- Convulsions
- Respiratory rate >60 breaths/min .
- Severe chest indrawing .
- Nasal flaring.
- Grunting .
- Buldging /depressed fontanelle.
- Discharge draining from the ear.
- Redness around umbilicus extending to the skin.
- Temperature .37.7˚C (or feels hot) or,35.5˚C(or feels cold).
- Lethargic or unconscious (not aroused by minimal stimulus).
- Reduced movements.
- Not able to feed (not able to sustain suck).
- Not attaching to the breast.
- No suckling at all.
- Crepitations.
- Cyanosis and
- Reduced digital capillary refill time.

Any of the signs listed above implies high suspicion of serious bacterial infection.

OR WITH

b) Maternal risk factors :

- Premature rupture of membranes.
- Prolonged labour (sum of 1^{st} and 2^{nd} stage of labour is >24 hours).
- Rupture of membranes (>24 hours).
- Maternal fever with evidence of bacterial infection within two weeks prior to delivery.
- Foul smelling or meconium stained liquor.
- Urinary tract infection.
- Caesarean section.
- Single unclean or more than 3 sterile vaginal examinations.
- Twin pregnancy.
- Invitro conception.
- Preclaamsia.
- Gestational diabetes mellitus.
- Cervical stitch insitu.

Exclusion criteria:

a) Neonates who had Birth asphyxia, Aspiration syndrome.

b) Laboratory findings which are suggestive of Inborn errors of metabolism

c) Neonates with Congenital anamolies .

d) Referred cases already treated with antibiotics.

DEFINITIONS[54]:

- Birth weight: The first weight of the newborn measured within the first hour of life.
- Low Birth Weight(LBW):Any neonate weighing less than 2500 grams(upto and including 2499 grams)
- Term neonate:from 37 completed weeks to less than 42 completed weeks (257 to 293 days)of gestation.
- Preterm neonate:less than 37 completed weeks (less than 259 days)of gestation.
- Septicemia: Neonatal sepsis is defined an invasive bacterial infection which occurs in the first 28 days of life[1] .
- Early Onset Sepsis: Sepsis diagnosed within first 72 hours of life.
- Late Onset Sepsis: Sepsis diagnosed beyond first 72 hours of life.

Ethical clearance: The study was approved from institutional ethics committee for Human Subject's Research, Jawaharlal Nehru Medical College, Belagavi.

Data collection: written informed consent was taken from the mother.

Sepsis work up included :

a) Blood culture to isolate the organism.
b) Estimation of Serum Procalcitonin Level.
c) Estimation of serial levels of C-Reactive Protein levels- 1st sample is collected at the time of admission before starting the antibiotics.2nd sample is collected after 72 hours of antibiotic administration.
d) Estimation of Haematological parameters: which included Haemoglobin, Total WBC counts and Platelet counts.

During the study period , over 36 neonates with suspected sepsis were admitted to the NICU and were recruited into this study.

Blood collection:

Blood from arterial and venous sample, finger or heelprick-capillary sampling and from newly inserted umbilical catheters can be used. The site of blood collection may also interfere with the blood culture result. Blood collected from umbilical artery catheter may allow contamination[(63)]. while blood collected from umbilicus vein catheter may be unreliable[(64)].

There is high risk of contamination with capillary blood sampling. To avoid these negative factors, blood for culture from peripheral vein by venipuncture remains the method of choice.

Blood was obtained from a peripheral vein in all the neonates with the help of trained staff under aseptic precautions in the present study.

For collection of blood, the skin at the peripheral vein puncture site was meticulously prepared by thoroughly cleaning with 70% ethyl alcohol and then by povidone -iodine. These bactericidal agents were applied in concentric circles moving outwards from the centre. To avoid the possible irritation of iodine it was wiped off with alcohol. The skin was then allowed to dry for 1 minute before the blood was withdrawn. Total of 3ml blood was collected.1 ml for blood culture to isolate the organism and remaining 2 ml for estimation of serum Procalcitonin , 1^{st} CRP level and for Haematological parameters. 0.5 ml of blood was collected after 72 hours of antibiotic administration for estimation of 2^{nd} CRP level .

Blood culture: All the blood samples were directly inoculated onto BD BACTEC Peds Plus/F culture vials and processed for microbial growth in radiometric culture BACTEC 460 TB, which works on the principle of detecting C_{14} labelled palmitic acid and measures quantitatively the radioactivity on a scale ranging from 0-999as a growth indicator.Positive cases were subjected to subculture and complete bacteriological identification was done with Microscan walkaway system which is an automated test system capable of microbial identification, antibiotic susceptibility testing, epidemiological trending and reporting[(65)].

Reagents:

The BD BACTEC Peds Plus/F culture vials contain the following active ingredients prior to processing:

Processed Water.....40 mL

Soybean-Casein Digest Broth .....2.75% w/v

Yeast Extract .....0.25% w/v

Animal Tissue Digest.....0.10% w/v

Sodium Pyruvate .....0.10% w/v

Dextrose .....0.06% w/v

Sucrose .....0.08% w/v

Hemin.....0.0005%w/v

Menadione.....0.00005% w/v

Sodium Polyanetholsulfonate (SPS) .....0.020% w/v

Pyridoxal HCl (Vitamin B6).....0.001% w/v

Nonionic Adsorbing Resin .....10.0% w/v

Cationic Exchange Resin .....0.6% w/v

All BD BACTEC media are dispensed with added CO2.

Procedure:1ml of blood sample to be tested is inoculated into the vial which is entered into the BACTEC instrument for incubation and periodic training. Each vial contains a sensor which responds to the concentration of CO2 produced by the metabolism of microorganisms or the consumption of oxygen needed for the growth of microorganisms. The sensor is monitored by the instrument very ten minutes for an increase in its fluorescence, which is proportional to the increasing amount of CO2 or the decreasing amount of O2 present in the vial.

The positive reading indicates the presumptive presence of viable microorganisms in the vial. This is followed with Microscan Walkaway system which is an automated test system capable of microbial identification, antibiotic susceptibility testing, epidemiological trending and reporting[(65)].

Advantages: include more rapid detection of pathogens, ability to monitor growth without visual inspection and automated handling of samples.

Quality control: Quality control requirements was performed in accordance with the laboratory's standard Quality Control procedures.

Serum Procalcitonin estimation: This test was done on serum samples using ROCHE COBAS 6000 fully integrated automatic analyser .

Principle: works on sandwich principle. It is a 2- step “sandwich” luminescence immunoassay using coated tubes and an acridine derived label that emits light in direct proportion to the PCT concentration.

Procedure: was performed as per the manufacturers literature.

RESULTS AND INTERPRETATION[54]: <0.5ng/ml-Normal

>=0.5ng/ml-Elevated

Serum C-Reactive Protein estimation: This test was done on serum samples by using ROCHE COBAS 6000 fully integrated automatic analyser.

Principle: It is a particle enhanced immunoturbudimetric assay. Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimertrically.

Procedure: was performed as per the manufacturers literature.

Interpretation[1] : <6mg/ltr- Normal.

>6mg/ltr-Elevated.

Haematological parameters:

Estimation of Haemoglobin, Total WBC counts and platelet counts was done in haematology laboratory ,of the department of pathology using MINDRAY-Automated haematology analyser.

Procedure: was performed as per the manufacturers literature.

Interpretation: Heamoglobin percentage: 13-19gms/dl-Normal

<13 or >19 gms/dl-Elevated.

Total WBC counts: 10,000 -26,0000 cells/mm^3-Normal

<10,000 or >26,0000 cells/mm^3-Elevated

Platelet counts: 1,00,000 -4,50,000 cells/mm^3-Normal

<1,00,000 or >4,50,000 cells/mm^3-Elevated

Statistical analysis:

Indices like Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value will be competed for each of the screening procedures :

Sensitivity: No .of true positive / No of true positive + no of false negative x 100 Specificity :No of true negative / No.of true negative+no false positive x 100

Positive predictive value: No of true positive/no.of no.of true positive + no of false positive1 x 100

Negative predictivevalue : No of true negative /no.of true negative+ no.of false negative x100

a) True positive: culture and test positive.

b) False negative: culture positive and test negative.

c) True negative: culture and test negative.

d) False negative: culture negative and test positive.

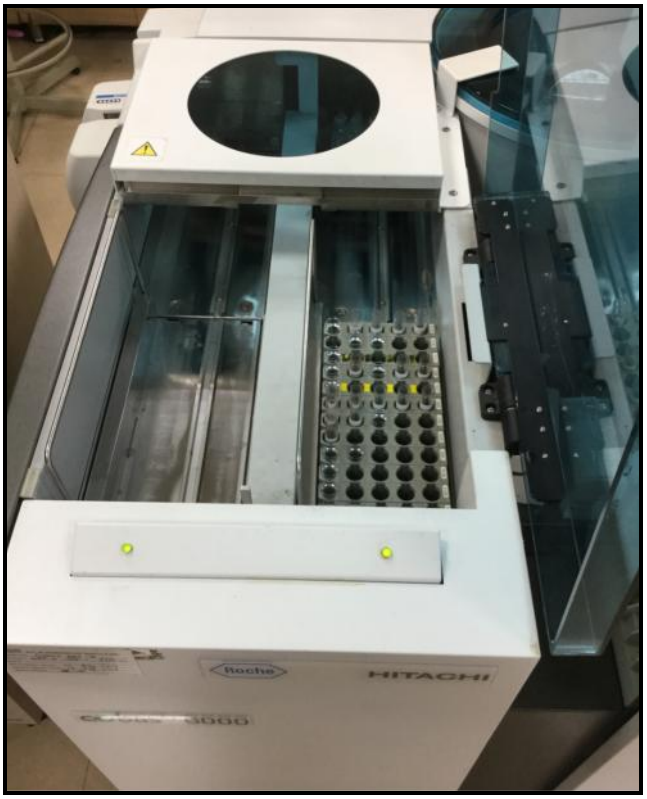
Photograph 1:Suspected case of neonatal sepsis

Photograph 2:Suspected case of neonatal sepsis

Photograph 3: Collection of blood sample for sepsis work up

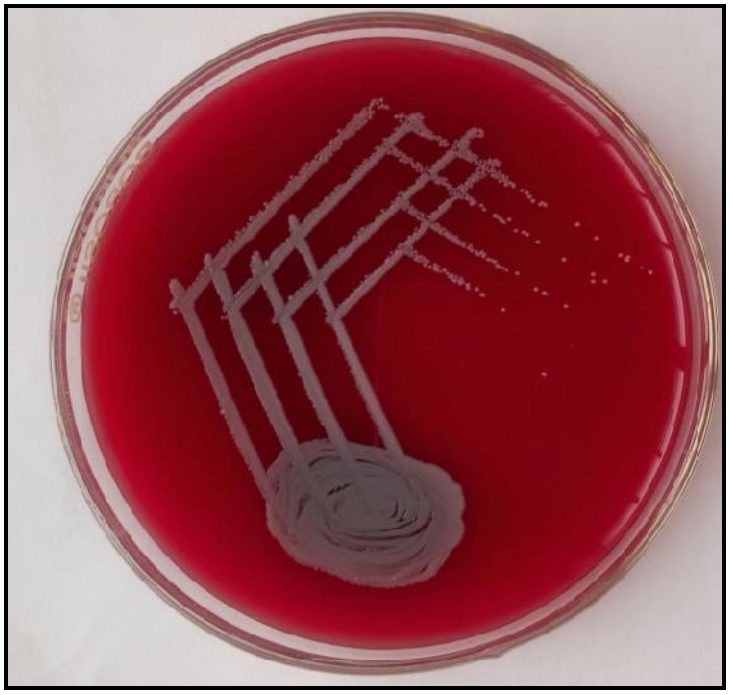
Photograph 4: Cobas analysers for quantitative measurement of serum procalcitonin and serum c-reactive protein

Photograph 5: Serum samples placed within the cobas analysers for quantitative measurement of serum procalcitonin and serum c-reactive protein



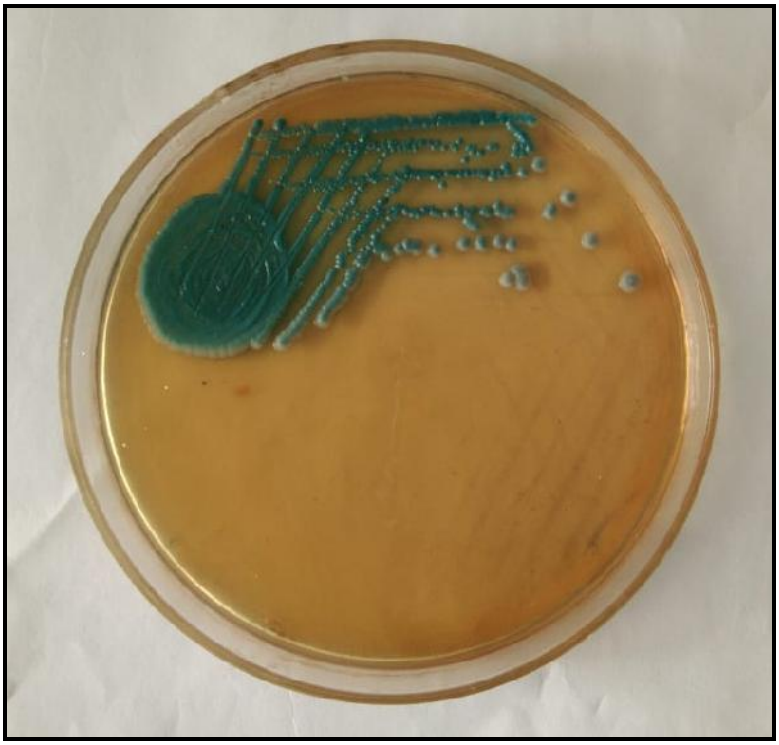
Photograph 6:Mucoid lactose fermenting colonies of *Klebsiella pneumoniae*

Photograph 7: Blood agar showing showing colonies of *Acinetobacter baumanii*.

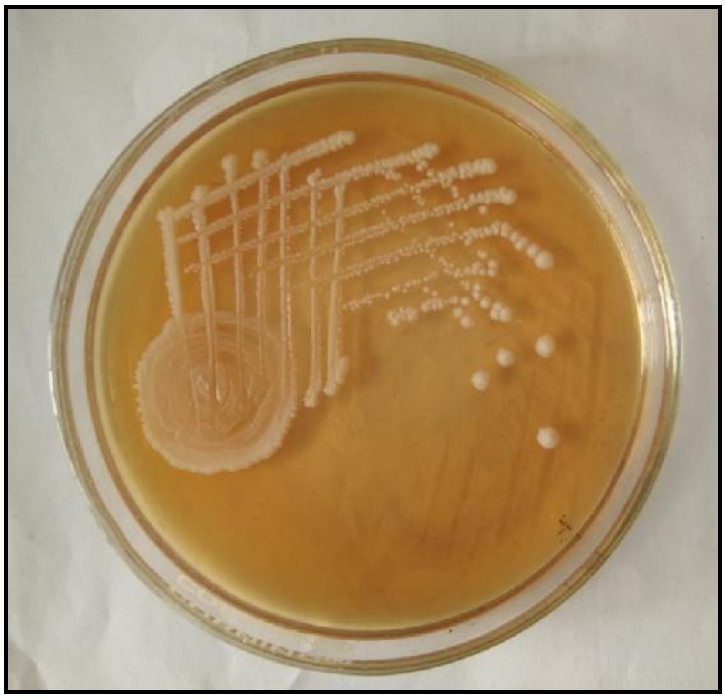


Circular, smooth, opaque, raised, non-hemolytic colonies.

Photograph 8: Hichrome agar showing *Candida tropicalis*



Photograph 9: Hichrome agar showing *Candida glabarta*



Photograph 10: Bactec 9050 Blood Culture System

Photograph 11: Microscan walkaway system

Photograph 12: BD bactec peds plus/f blood culture vial:

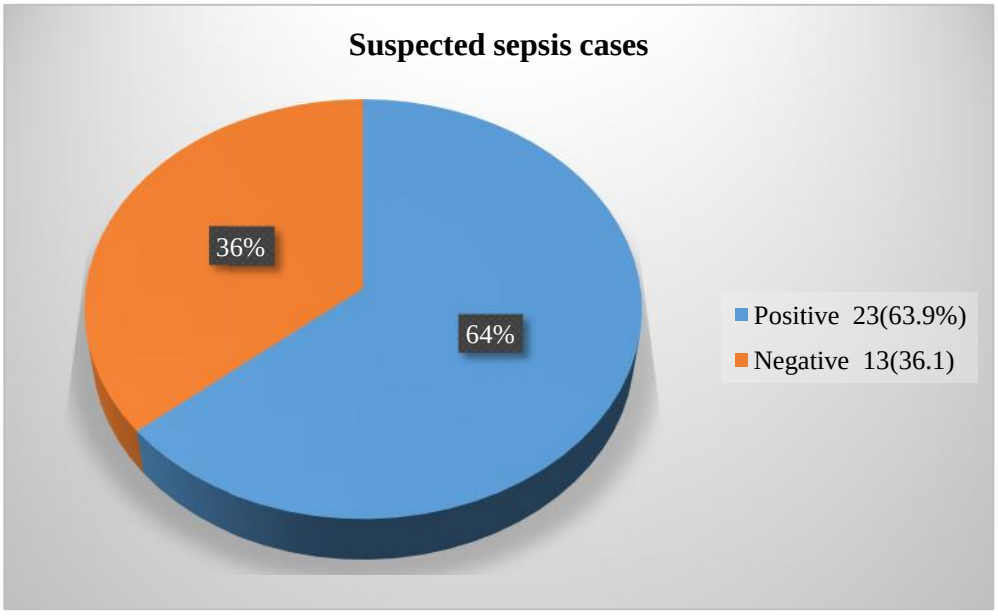
RESULTS:

BLOOD CULTURE POSITIVITY RATE:

Table no 1: Blood Culture Positivity Rate:

Blood culture	Suspected sepsis cases (n=36)
Positive	23(63.88%)
Negative	13(36.12%)
Total	36(100%)

Graph no 1: Blood Culture Positivity Rate



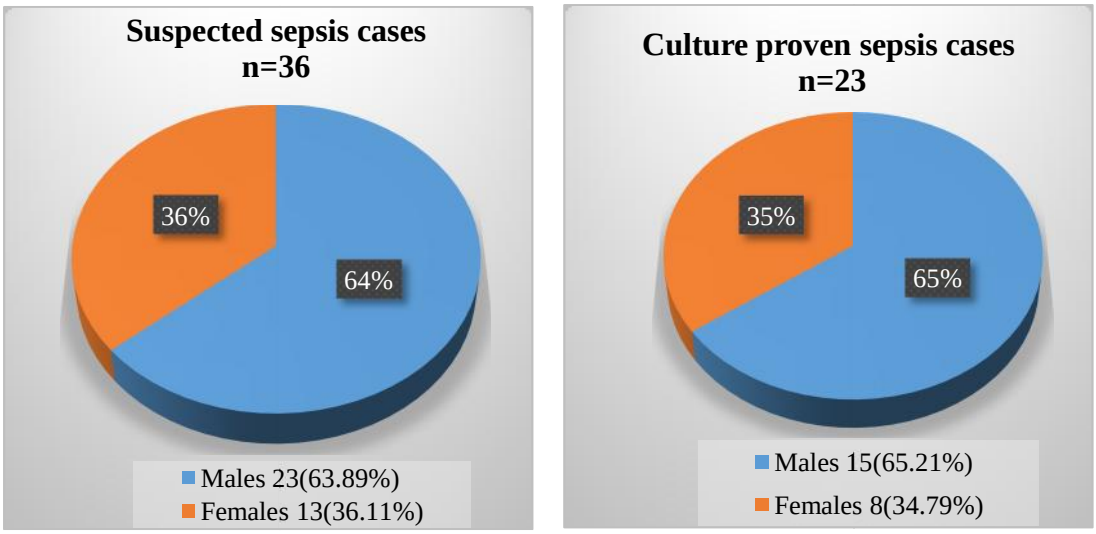
In the present study, blood culture was positive in 63.89% (n=23) of suspected sepsis cases and was negative in 36.1%(n=1) cases. Hence the blood culture positivity rate in the present study was 63.89%.

GENDERWISE DISTRIBUTION OF SEPSIS:

Table no 2: Genderwise Distribution Of Sepsis:

Gender	Suspected sepsis cases(n=36)	Culture proven sepsis cases(n=23)
Male	63.89% (23)	65.21%(n=15)
Female	36.11%(13)	34.79%(n=08)
Total	100%(36)	100%(n=23)

Graph no 2: Genderwise Distribution Of Sepsis:



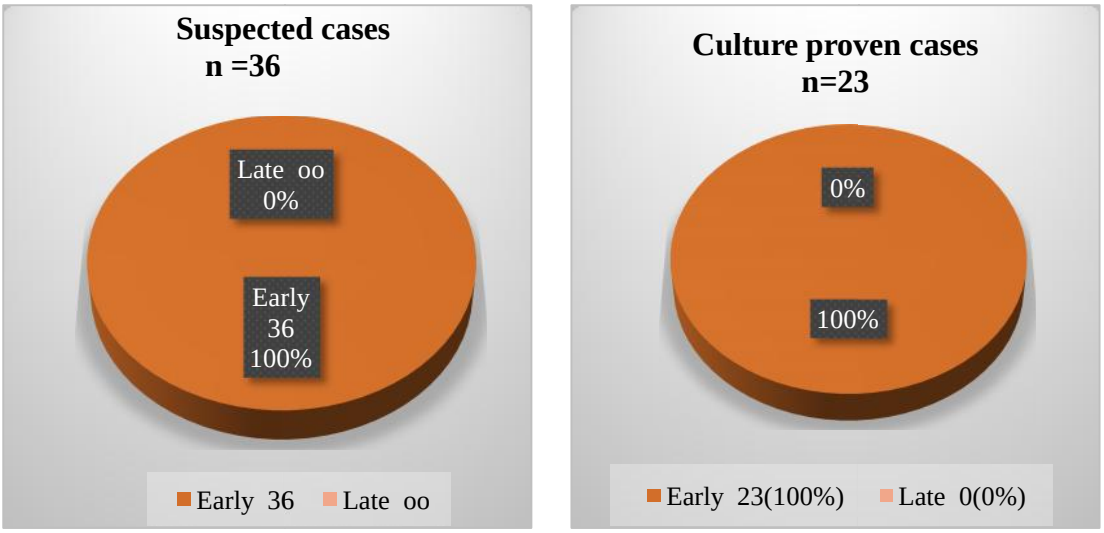
The Male: Female ratio of the neonates included in this study was 1.76:1. Out of 23 Culture proven sepsis cases ,prevalence was significantly more in male neonates 65.21%(n=15) than females neonates 34.79%(n=08).

DISTRIBUTION OF SEPSIS DEPENDING ON ONSET OF SEPSIS:

Table no 3:Distributuion of sepsis depending on the onset of sepsis

Onset	Suspected sepsis cases (n=36)	Culture proven sepsis cases (n=23)
Early	36(100%)	23(100%)
Late	00(00%)	00(00%)

Graph no 3: Distributuion of sepsis depending on the onset of sepsis:



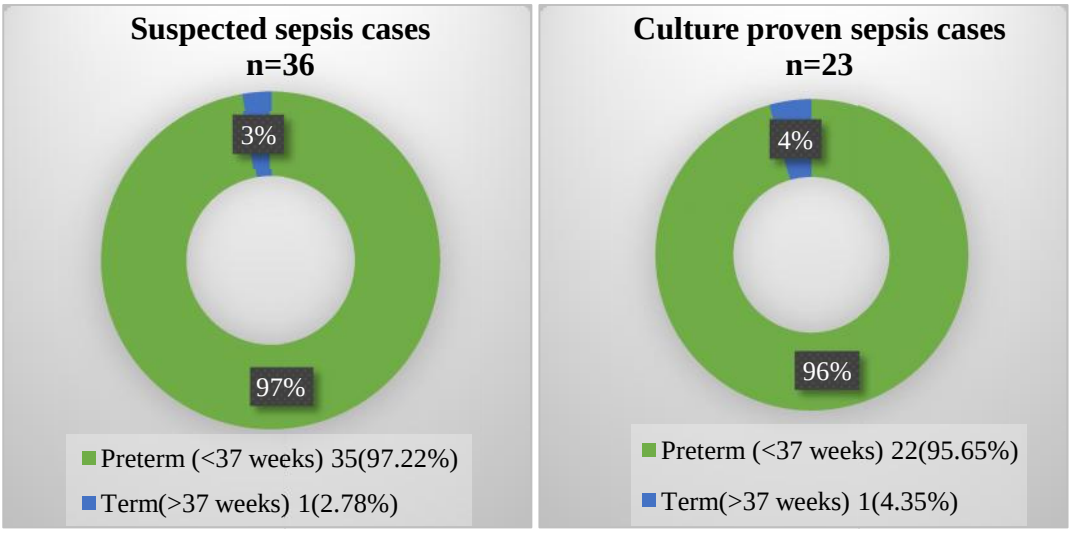
Neonates who fulfilled the inclusion criteria belonged to early onset sepsis group. Hence there were no cases of late onset sepsis .

DISTRIBUTION OF SEPSIS ACCORDING TO GESTATIONAL AGE:

Table no 4 : Distribution of sepsis according to gestational age:

Gestational age	Suspected sepsis cases n=36	Culture proven sepsis cases n=23
Preterm(<37 weeks)	97.22%(n=35)	95.65%(n=22)
Term (>37 weeks)	2.78%(n=010	4.35%(n=01)
Total	100%(n=36)	100%(n=23)

Graph no 4: Distribution Of Sepsis According To Gestational Age:



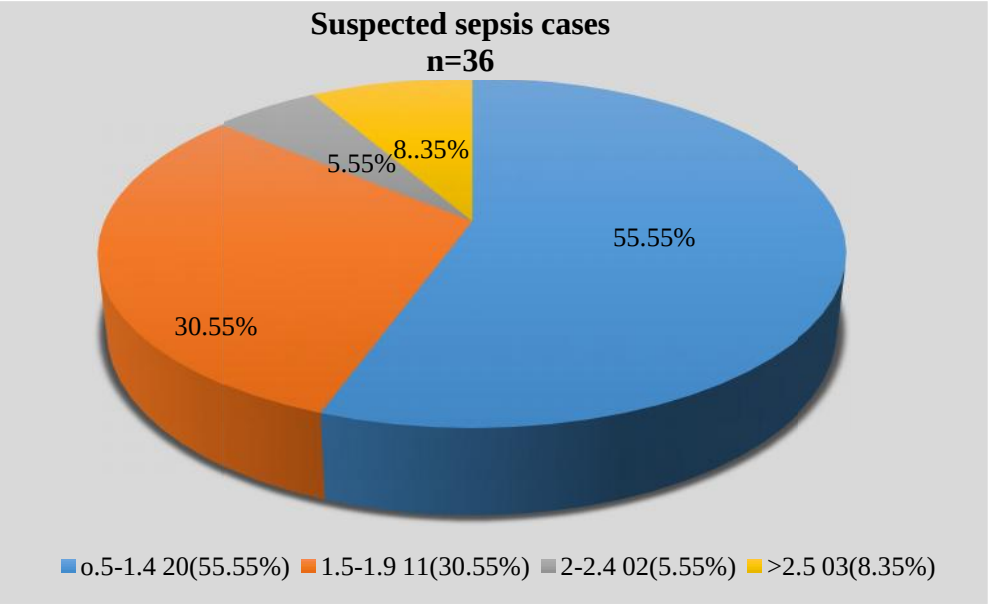
Out of 36 suspected sepsis, 2.78% (n=01) was term neonate and 97.22% (n=35) were preterm neonates. Out of 23 culture proven sepsis, 4.35% (n=01) was term and neonate95.65%(n=22) were preterm.

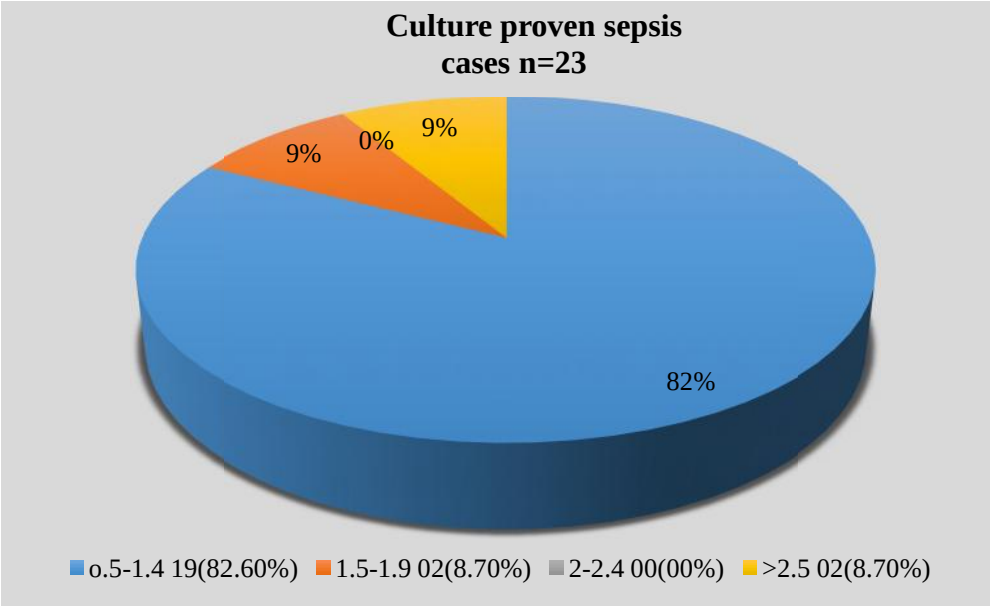
DISTRIBUTION OF SEPSIS ACCORDING TO BIRTH WEIGHT:

Table no 5: Distribution Of Sepsis According To Birth Weight:

Birth weight in Kilograms	Suspected sepsis cases(n=36)	Culture proven sepsis cases(n=23)
0.5-1.4	55.55%(n=20)	82.60%(n=19)
1.5-1.9	30.55%(n=11)	8.70%(n=02)
2-2.4	5.55%(n=02)	00%(n=00)
>2.5	8.35%(n=03)	8.70%(n=02)
Total	100%(n=36)	100%(n=23)

Graph no 5: Distribution Of Sepsis According To Birth Weigh





Out of 36 neonates with suspected sepsis 91.65%(n=33) neonates were of low birth weight (<2500 gm) and 8.35% (n=03) neonates were of normal birth weight.out of 23 neonates with culture proven sepsis 91.3%(n=21) neonates were of low birth weight and 8.70%(n=02) neonates were of normal birth weight. Out of the culture proven sepsis cases, Culture positivity was highest amongst low birth weight neonates 91.3%(n=21). Only 8.70%(n=02) neonates with normal birth weight showed culture positivity.

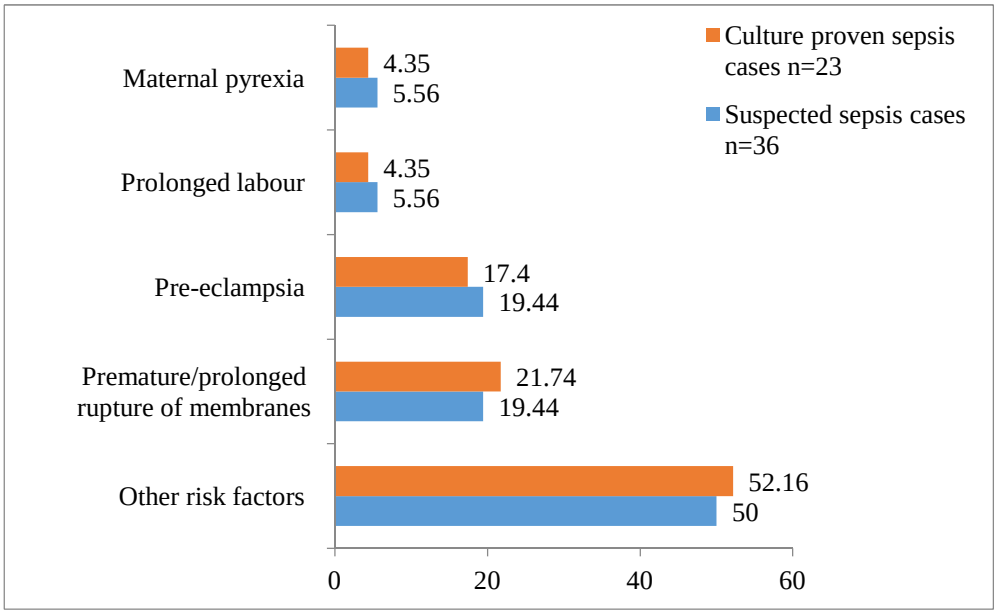
In this study there was no significant difference in rate of culture isolation among the neonates based on the parity of the mother.

SEPSIS IN RELATION TO MATERNAL RISK FACTORS:

Table no 6: Sepsis In Relation To Maternal Risk Factors:

Maternal Risk factors	Suspected sepsis cases(n=36)	Culture proven sepsis cases(n=23)
Premature/prolonged rupture of menbranes	19.44%(n=07)	21.74%(n=05)
Prolonged labour	5.56%(n=02)	4.35%(n=01)
Preeclampsia	19.44%(n=07)	17.40%(n=04)
Maternal pyrexia	5.56%(n=02)	4.35%(n=01)
Maternal UTI	00%(n=00)	00%(n=00)
Unclean vaginal examinations	00%(n=00)	00%(n=00)
others	50%(n=18)	52.16%(n=12)
Total	100%(n=36)	100%(n=23)

Graph no 6: Sepsis In Relation To Maternal Risk Factors:



Out of the 23 culture proven sepsis cases, highest number of cases had premature/prolonged rupture of membrane 21.74% as the maternal risk factor followed by pre-eclamsia 17.40%,prolonged labour 4.35% and maternal pyrexia 4.35%.

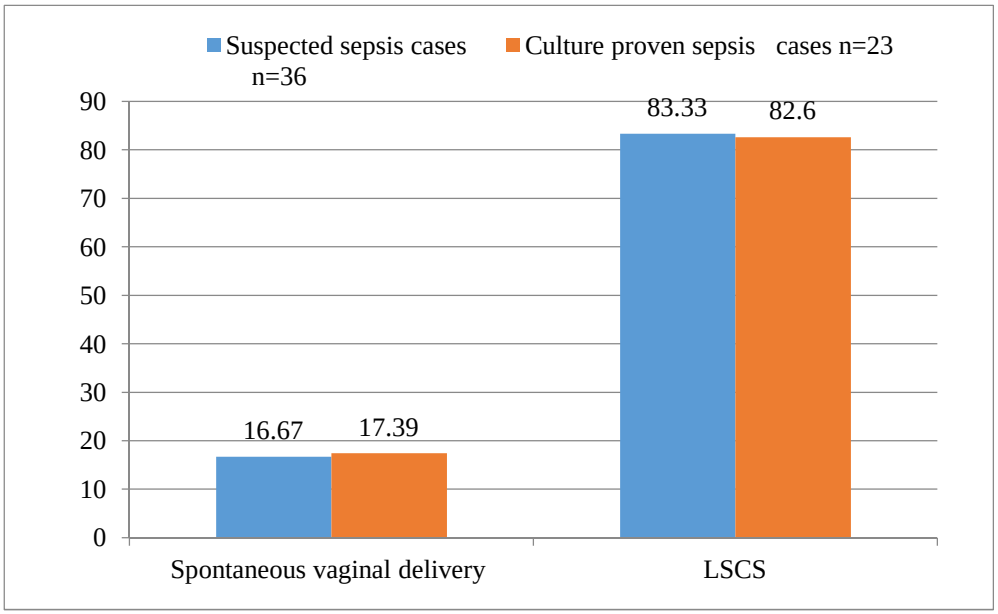
52.16% of the cases accounted to other risk factors like Twin pregnancy,Invitro conception,Gestational diabetes mellitus,Cervical stitch insitu,home delivery,cervical encirclage etc

SEPSIS IN RELATION TO MODE OF DELIVERY:

Table no 7: Sepsis In Relation To Mode Of Delivery:

Mode of delivery	Suspected sepsis cases (n=36)	Culture proven sepsis cases (n=23)
Spontaneous vaginal delivery	6(16.67%)	04(17.39%)
LSCS	30(83.33%)	19(82.60%)

Graph no 7: Sepsis In Relation To Mode Of Delivery:



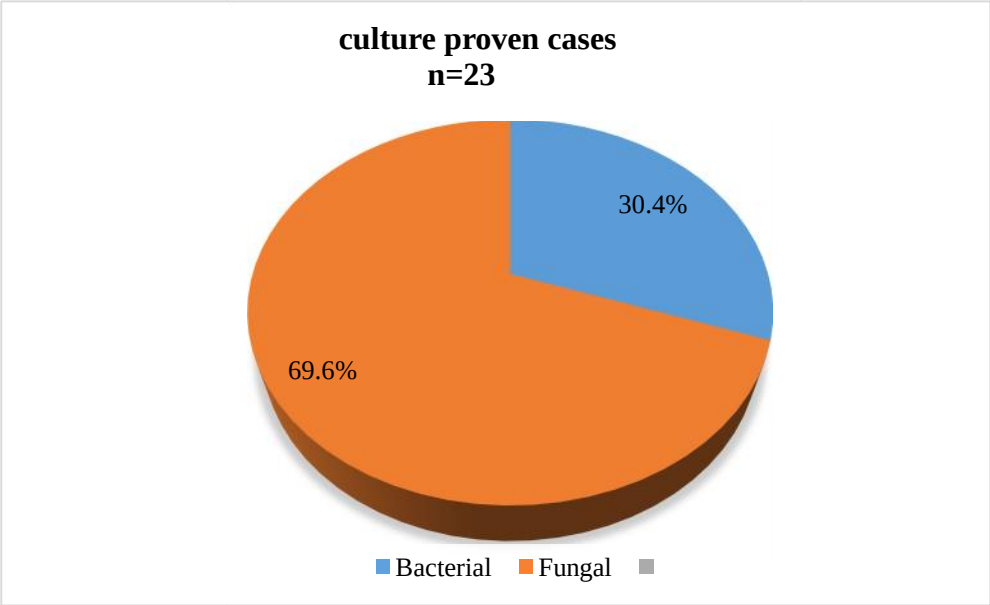
Among the 36 suspected cases of neonatal sepsis, 16.67% (n=06) were delivered by normal vaginal delivery (NVD), and 83.33% (n=30) by lower section caesarean section (LSCS). Among the 23 culture positive cases of neonatal sepsis,17.39% (n=04) were delivered by normal vaginal delivery (NVD), and 82.60%(n=19) by lower section caesarean section. About four fold raise in culture positivity was noticed among the neonates delivered by LSCS (82.60%) in comparison to those delivered by NVD (17.39%)

BLOOD CULTURE ISOLATE TYPE:

Table no 8: Blood Culture Isolate Type:

Blood culture isolate type	Culture proven sepsis cases (n=23)
Bacterial	07(30.44%)
Fungal	16(69.44%)
Total	23(100%)

Graph no 8: Blood Culture Isolate Type:



Out of 23 culture proven sepsis cases 30.44%(n=07) were bacterial isolates and 69.44%(n=16) were fungal isolates. there was a two fold rise in fungal isolates compared to bacterial isolates in the present study.

DISTRIBUTION OF THE CULTURE ISOLATES:

Table no 9: Distribution Of The Culture Isolates:

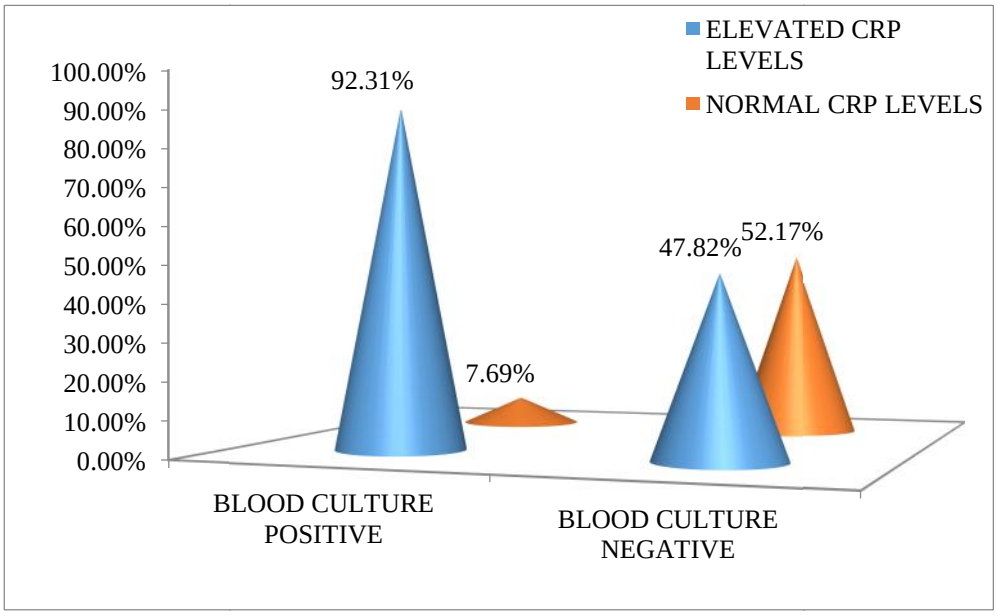
Sr.no	Organism	No.of isolates(n=23)
1	Candida glabrata	34.78%(n=08)
2	Candida tropicalis	30.43%(n=07)
3	Candida cruzi	4.35%(n=01)
4	Klebsiella pneumonia	8.09%(n=02)
5	Pseudomonas aeruginosa	4.35%(n=01)
6	Escherichia coli	4.35%(n=01)
7	Enterobacter species	4.35%(n=01)
8	Staphylococcuc epidermidis	4.35%(n=01)
9	Staphylococcus haemolyticus	4.35%(n=01)
Total		100%(n=23)

Among the fungal isolates, Candida glabrata 34.78% (n=8) constituted majority of isolates followed by Candida tropicalis 30.43%(n=7) and Candida cruzi 4.35%(n=01). Among the bacterial isolates Klebsiella pneumoniae constituted majority of isolates 8.09%(n=2) followed by Pseudomonas aeruginosa 4.35%(n=1),Escherichia coli 4.35%(n=1), Enterobacter cloacae 4.35%(n=1),), Staphylococcus epidermidis 4.35%(n=1),Staphylococcus haemolyticus 4.35%(n=1).

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF 1ST CRP level:

In the present study, out of 23 blood culture positive cases, 92.31% showed elevated crp levels whereas 7.69% showed normal CRP levels. out of 13 blood culture negative cases 47.82% showed elevated CRP levels and 52.17% showed normal CRP levels. The sensitivity of CRP was 50% and the specificity was noted to be highest which was 92.30%. The positive and negative predictive values were found to be 92.30 % and 52.17 % respectively.

Graph no 9: Sensitivity, Specificity, Positive Predictive Value And Negative Predictive Value Of 1st Crp Level:



Sensitivity:50
Specificity:92.30
PPV:92.30
NPV:52.17

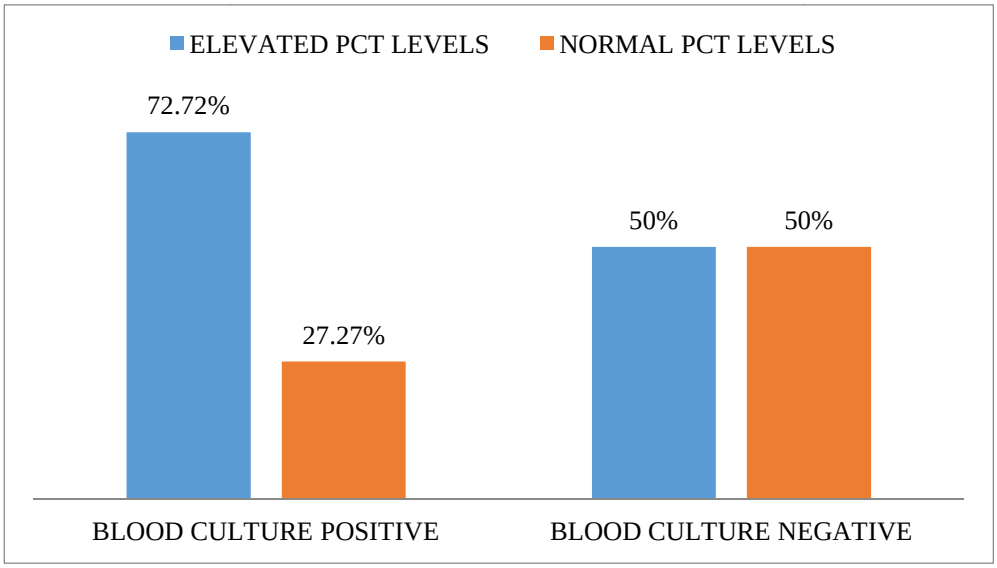
SERIAL LEVELS OF C-Reactive Protein:

In the present study, there was persistent increase in the CRP seen in all the suspected and culture proven cases of neonatal sepsis which was done after 72 hours of antibiotic administration.

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF PROCALCITONIN:

In the present study, out of 23 blood culture positive cases, elevated PCT levels was seen in 72.72% cases and showed normal levels in 27.27%.out of 13 blood culture negative cases,50% showed elevated PCT levels and 50% showed normal PCT levels. PCT had highest sensitivity of 69.56% and specificity of 53.84%. The positive predictive value was found to be 72.72% and the negative predictive value was 50%.

Graph no 10: Sensitivity,Specificity,Positive Predictive Value And Negative Predictive Value Of Procalcitonin



Sensitivity:69.56
Specificity:53.84
PPV:72.72
NPV:50

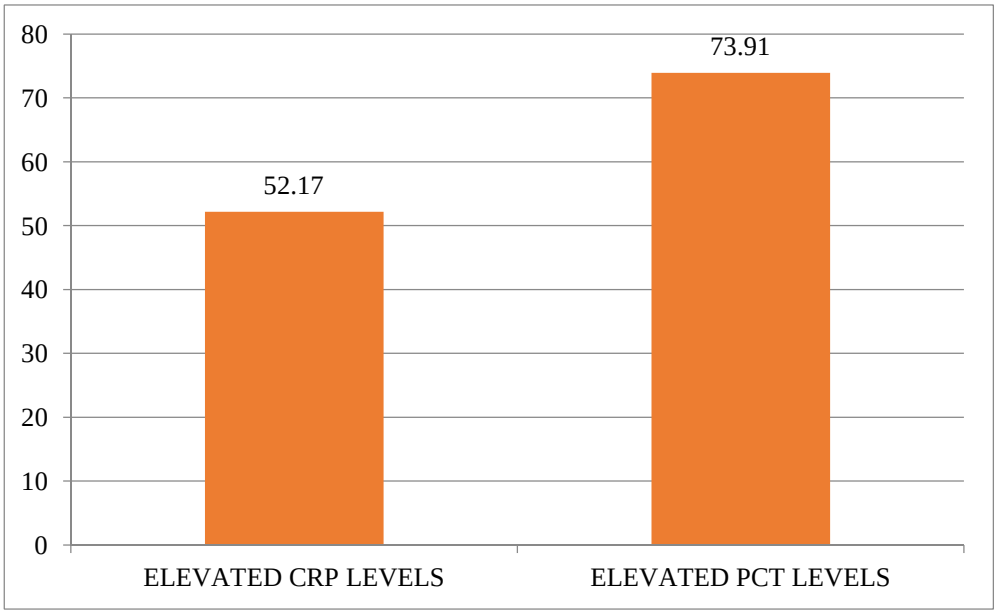
COMPARISION OF 1ST CRP AND PROCALCITONIN LEVELS:

In the present study, out of 23 culture proven sepsis cases ,elevated CRP levels was noted in 52.17% cases whereas elevated PCT levels was noted in 73.91% of cases.

Table no10: Comparision Of 1st Crp And Procalcitonin Levels:

Markers	Suspected sepsis cases	Culture proven sepsis cases
1ST CRP	13(36.11%)	12(52.17%)
PCT	24(66.66%)	17(73.91%)

Graph no 11: Comparision Of Elevated Crp And Pct Levels In Culture Proven Sepsis Cases:

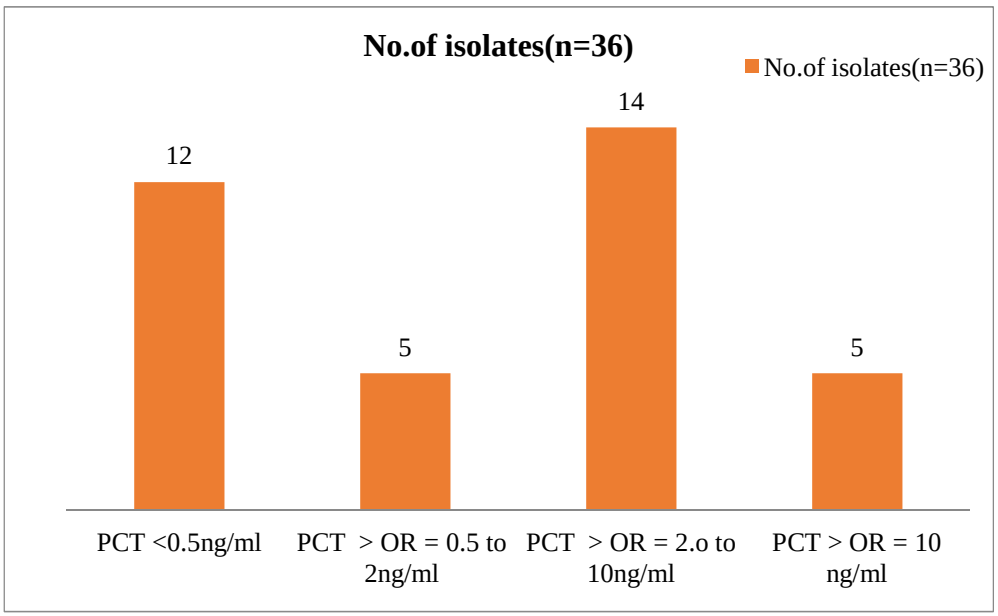


INTERPRETATION OF PCT LEVELS IN SUSPECTED SEPSIS CASES:

Table no 11: Interpretation Of Pct Levels In Suspected Sepsis Cases:

PCT levels range	Interpretation	No.of isolates
0.5ng/ml	Local bacterial infection is possible, systemic infection(sepsis)is not likely	12
≥ 0.5ng/ml	Systemic infection is possible.moderate risk of progression for progression to severe systemic infection	05
≥2 – 10 ng/ml	Systemic infection is likely, unless other causes are known, high risk of progression to severe systemic infection.	14
≥ 10 ng/ml	Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis. High likelihood of severe bacterial sepsis.	05

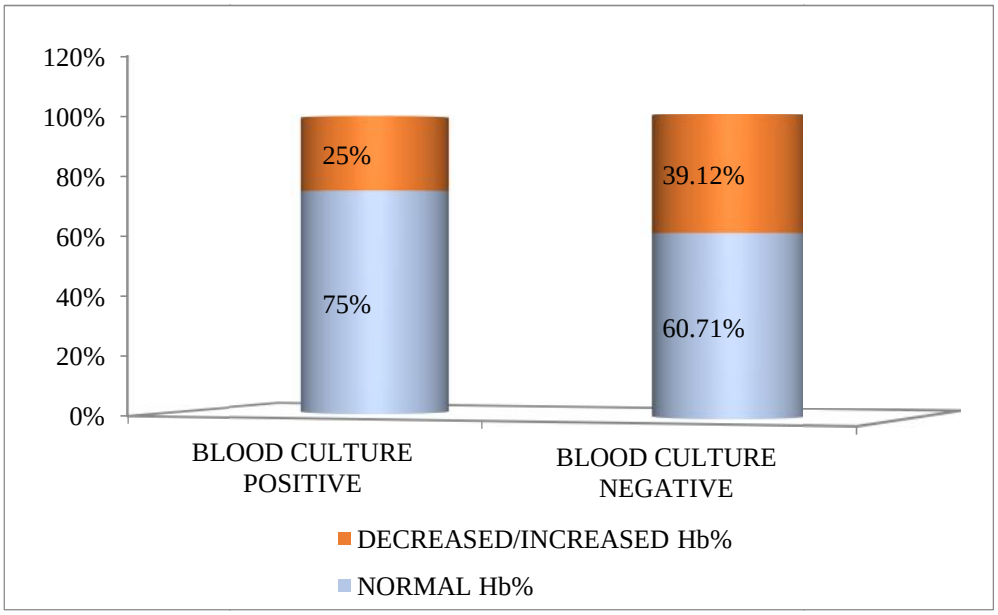
Graph no 12: Interpretation Of Pct Levels In Suspected Sepsis Cases:



SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF HAEMOGLOBIN LEVELS:

In the present study, out of 23 blood culture positive cases 25% showed altered haemoglobin percentage where as 75%m showed normal haemoglobin percentage.out of 13 blood culture negative cases 39.12% cases showed altered where as 60.71% showed normal haemoglobin percentage. The sensitivity of haemoglobin percentage was 26.06% and specificity was 84.61%.positive predictive value was 75% and negative predictive value was 39.23%.

Graph no 13: Sensitivity, Specificity, Positive Predictive Value And Negative Predictive Value Of Haemoglobin Levels:

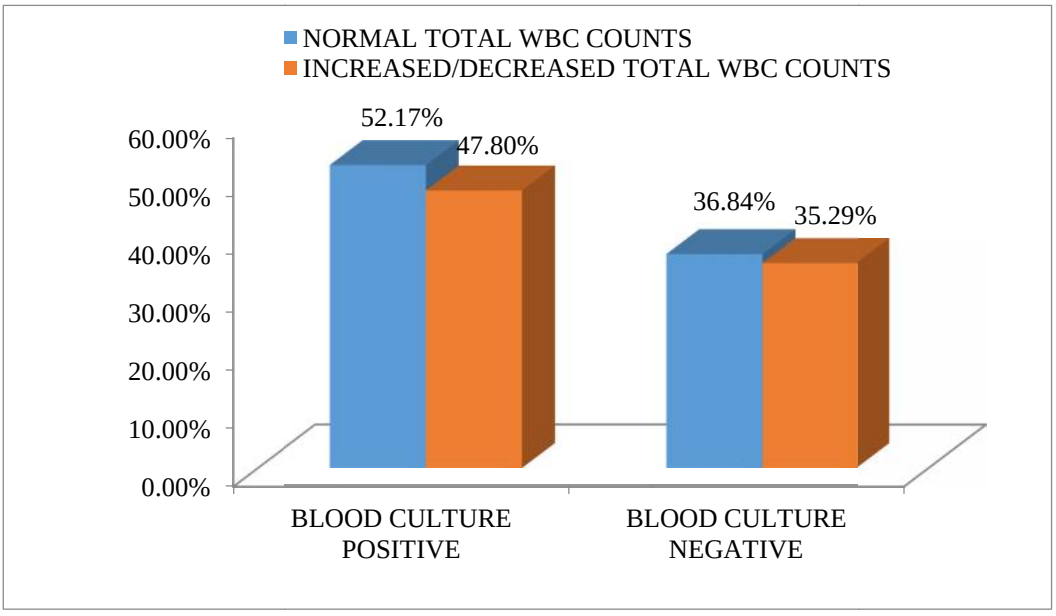


Sensitivity:26.06
Specificity:84.61
PPV:75
NPV:39.28

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF TOTAL WBC COUNTS:

In the present study, out of 23 blood culture positive cases 47.80% showed altered total WBC counts where as 52.17% showed normal total WBC counts.out of 13 blood culture negative cases 35.29% cases showed altered where as 36.84% showed normal total WBC counts. Total WBC counts showed the sensitivity of 61.11% and the specificity was found to be 53.84%. The positive predictive value and negative predictive values were 64.70% and 63.15% respectively.

Graph no 14: Sensitivity, Specificity, Positive Predictive Value And Negative Predictive Value Of Total Wbc Counts

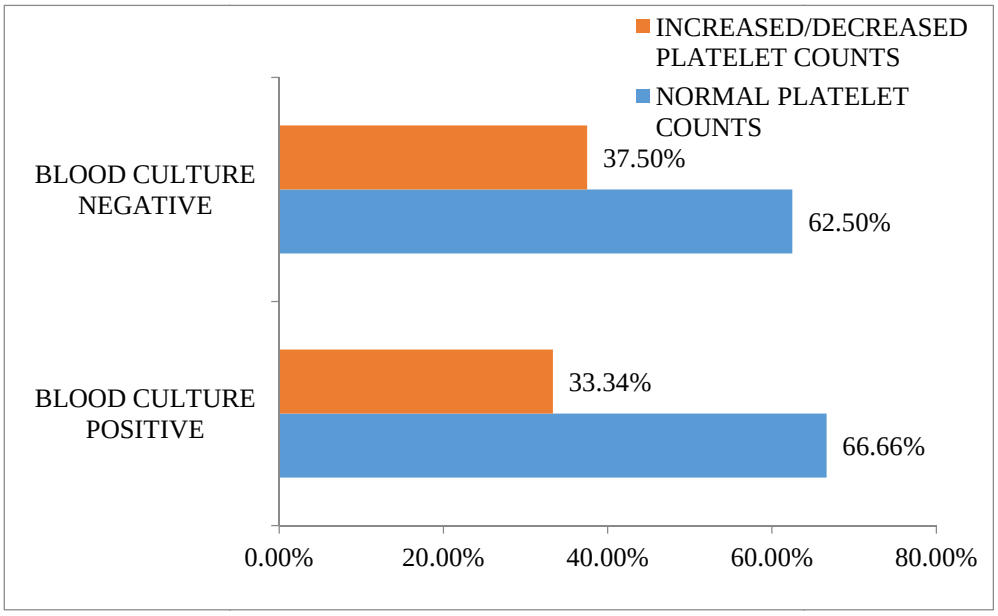


Sensitivity:61.11
Specificity:53.84
PPV:64.70
NPV:63.15

SENSITIVITY,SPECIFICITY,POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF PLATELET COUNTS:

In the present study, out of 23 blood culture positive cases 33.34% showed altered platelet counts where as 66.66% showed normal platelet counts. out of 13 blood culture negative cases 37.50% cases showed altered platelet counts where as 62.50% showed normal platelet counts. The sensitivity of platelet counts was 47.05% and specificity was 69.25%.positive predictive value was 66.66 % and negative predictive value was 37.5%

Graph no 15: Sensitivity, Specificity, Positive Predictive Value And Negative Predictive Value Of Platelet Counts



Sensitivity:47.05
Specificity:69.25
PPV:66.66
NPV:37.5

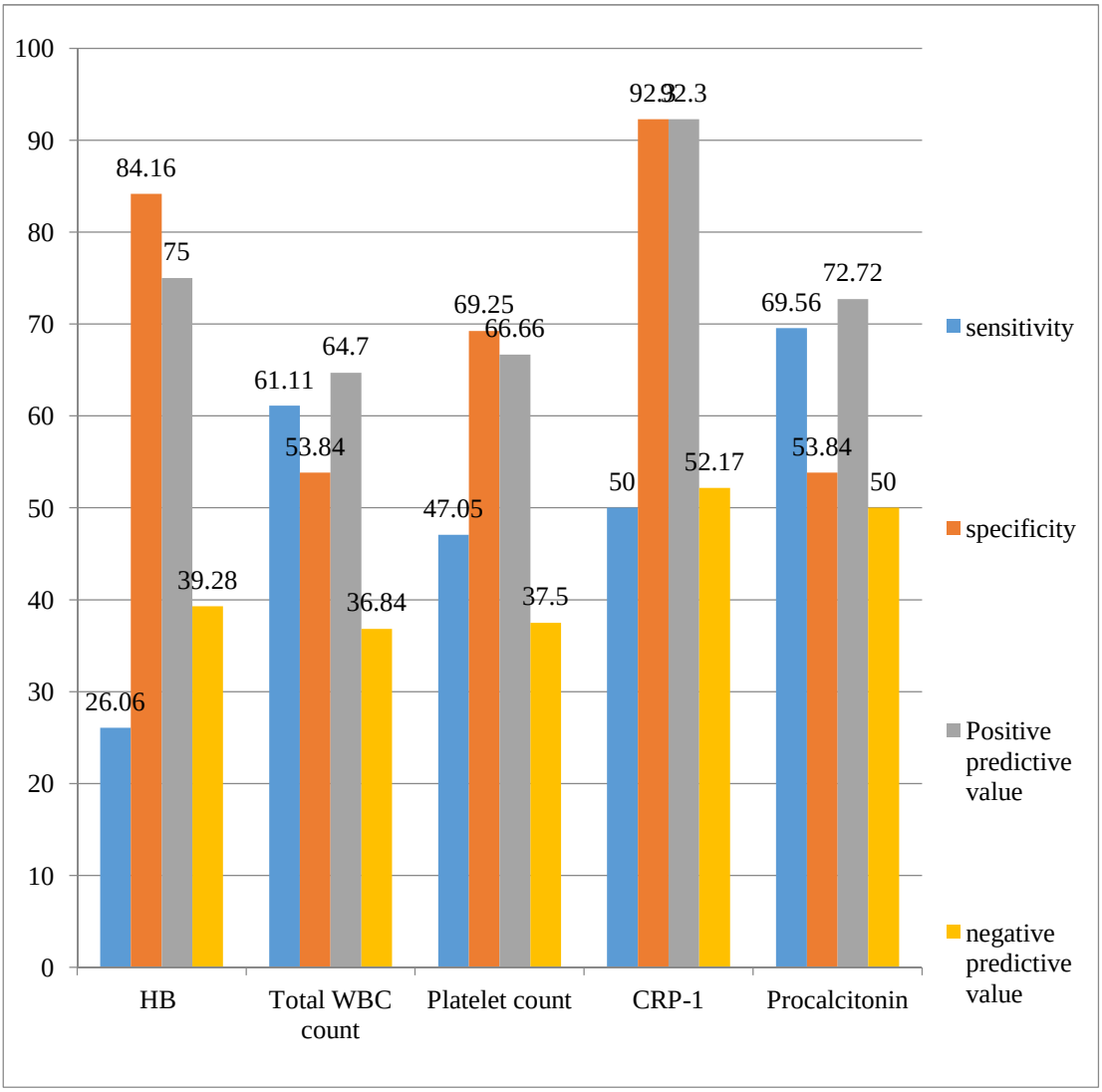
COMPARISION OF ALL THE MARKERS OF SEPSIS:

Among all the markers of sepsis in the present study, procalcitonin showed the highest sensitivity 69.56% and c-reactive protein showed the highest specificity of 92.30%.CRP showed the highest positive predictive value of 92.30% followed by PCT which is 72.72%.Total WBC counts showed the least negative predictive value of 36.84%.

Table no 12: Comparision Of All The Markers Of Sepsis:

Markers	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Haemoglobin percentage	26.06%	84.16%	75%	39.28%
Total WBC counts	61.11%	53.84%	64.70%	36.84%
Platelet counts	47.05%	69.25%	66.66%	37.5%
1st CRP	50%	92.30%	92.30%	52.17%
Procalcitonin	69.56%	53.84%	72.72%	50%

Graph no 16: Comparision Of All The Markers Of Sepsis:



DISCUSSION

Neonatal septicemia is a clinical syndrome characterized by systemic signs of infection in the first month of life. It is the leading cause of neonatal morbidity and mortality in our country. Many perinatal risk factors predispose neonates to sepsis, which can be prevented by timely intervention. Further, the identification of microorganisms in patient's blood is very important to know the nature of microorganisms and antibiotic susceptibility ;so as to treat promptly.

The present study was therefore undertaken to effectively diagnose sepsis at the earliest and evaluate the same and to assess the efficacy of limited rapid diagnostic tests in comparision with the blood culture, which is considered as gold standard in the diagnosis of sepsis.

BLOOD CULTURE POSITIVITY RATE:

In the present study, total of 36 suspected neonatal sepsis were included out of which 23 were positive for blood culture, accounting to the blood culture positivity rate of 63.88%.

Several studies have been undertaken on bacteriological profile in neonatal septicemia in our country. The table given below shows culture positivity rate of different workers across the country.

Table: Blood Culture Positivity Rate In Neonatal Septicemia By Various Other Studies:

SR.NO	AUTHOR	PLACE OF STUDY	YEAR	PERCENTAGE POSITIVITY
1	Vinodkumar et al[66]	Gulbarga	2008	53.2%
2	Zakariya et al[47]	South india	2011	41.6%
3	Desai et al[67]	Bhavnagar	2010	46.2%
4	Gosalia et al[68]	Rajkot	2013	62%
5	Jadhav et al[69]	Pune	2013	65.2%
6	Sonawane et al[70]	Nashik	2015	49.09%
7	Singh et al[71]	Raipur	2016	57.2%
8	Present study	Belagavi	2018	63.88

From the table above it is evident that blood culture positivity rate ranged from 40%-65%. The positivity rate of present study is comparable with that encountered by Jadhav et al[69] -65.2% , Gosalia et al-[68]-62%,Singh et al[71] -57.2%.

The wide range in the incidence of culture proven sepsis could be related to the total number of suspected sepsis cases.

The variation in the rate of isolation in different studies can be attributed to the fact that the incidence of neonatal sepsis varies from place to place under the influence of various factors like gestational age, birth weight of the neonate, maternal nutrition, perinatal care, health care facilities etc.

Though bacteria are the most common agents implicated to cause sepsis, organisms like adeno virus, enterovirus, rubella and coxsackie viruses, Toxoplasma and Candida species which are the other causative organisms of sepsis in neonates may add up to cause the discrepancy in rate of culture isolation.

The site of blood collection may also interfere with the blood culture result. Blood collected from umbilical artery catheter may allow contamination[63] while blood collected from umbilicus vein catheter may be unreliable[64].To avoid these negative factors blood for culture was obtained from a peripheral vein in all the neonates with the help of trained staff in the present study.

GENDERWISE DISTRIBUTION OF SEPSIS:

The Male: Female ratio of the neonates included in this study was 1.76:1.

Out of Most of the studies reported male predominance kumhar et al[72] reported 76.02%,Sharma et al[73] reported 62.08% and Jyothi et al [38]reported 65.5%.

The probable reason for male predominance could be that the factors regulating the synthesis of gamma globulin are probably situated on the X chromosome. Presence of one X-chromosome in the male neonates confers less immunological protection compared to the females. It could also be because of importance given to male neonates and also because of more number of male neonates born compared to female neonates.

ONSET OF SEPSIS:

Incidence of early onset sepsis was signifinantly high i.e 100% in both suspected and culture proven sepsis cases as compared to late onset sepsis in our

study which is in consistent with the studies done by Movahedian AH et al[27] ,Rasul C.H et al [74], Waseem R et al [39],Aletayab et al [75] and Al-Shamahy et al [76] .The time period of early onset ranged from 0 to 72 hours in the present study.

The lower incidence of LOS in this study cannot be explained by a single factor. Various changes that have occurred in the recent years in addition to the increased awareness in prevention of sepsis like better hand hygiene practices, maintaining standard protocols in handling intravenous catheters and shorter duration of invasive ventilation due to the use of surfactants could have contributed to the decreased incidence of LOS.

According to most of the studies done ,Early onset sepsis is generally acquired by the new born vertically, during birth, from endogenous bacteria in the maternal reproductive tract.

SEPSIS IN RELATION TO BIRTH WEIGHT AND GESTATIONAL AGE:

In the present study, Culture proven sepsis was more common among the preterm and low birth weight babies. Similar findings were reported in various studies including Dhumal et al[1] , Vergnano et al [2] , Woldu MA et al [3] and Mutlu et al [4].A very strong association of culture proven sepsis (94%) with prematurity was reported by Chauhan Setal B et al[5] .

LBW and preterm neonates are at high risk of developing sepsis in comparison to a term neonate as they are vulnerable to sepsis due to their intrinsic susceptibility to infection owing to the immature immune system,in addition to other factors like deficient IgG levels prolonged hospital stay, total parenteral nutrition and exposure to invasive procedures.

Placental transport of IgG from maternal to fetal circulation increases with maturity. However, this transport is hampered in low birth weight and preterm infants who are often products of placental insufficiency[5].

SEPSIS IN RELATION TO MATERNAL RISK FACTORS:

Out of the 23 culture proven sepsis cases, highest number of cases had premature/prolonged rupture of membrane 21.74% as the maternal risk factor followed by preclamsia 17.40%,prolonged labour 4.35% and maternal pyrexia 4.35%.

Similar findings were observed in studies done by Tallur et al[75],Roy et al[77],Chacko et al[28],Vinodkumar et al[66], Garg et al[78], Bhat et al[79], and Gandhi et al [80].

Several studies have observed that babies born to mothers with pre-eclampsia during the antenatal period were at a higher risk of developing early onset sepsis . Doron et al[81] opined that 40%-50% of neonates whose mothers had pre-eclampsia , have neutropenia that generally resolves after 72 hours of birth.the neutropenia in these neonates predispose them to early neonatal infections. Prolonged rupture of membranes for more than 24 hours was seen as the most common factor putting the newborns at the risk to develop sepsis.vesikari et al [81] similarily found that PROM of more than 24 hours before delivery was seen in mothers whose babies developed symptoms of sepsis in the first 24 hours.

When there is rupture of amniotic membrane ,organisms colonizing the vagina gain access into the uterine cavity and contaminate both amniotic fluid and the fetus.this leads to development of neonatal sepsis after birth[81].this is common

obstretic complication which poses the health hazard to the fetus,is often overlooked,specially in overworked obstretic centres.

Maternal pyrexia was seen in 4.35% of the culture proven sepsis cases in the present study.kousar et al[82] observed that 8.4% of mothers had maternal pyrexia during the antenatal period and their babies subsequently developed neonatal septicemia.Tallur et al in their study, observed 4.13% mothers had intrapartum fever.significant association was also observed by samsigina et al[22].chacko et al[28], however ,observed that there was no association between peripartum fever in the mother and increased sepsis in the neonates.

In the absence of maternal risk factors,neonates could be at a risk of sepsis ,due to prematurity,low birth weight,small for gestational age, or neonatal asphyxia.

SEPSIS IN RELATION TO MODE OF DELIVERY:

Further in this study, a significant proportion of culture proven sepsis was found to be associated with LSCS.

Similar findings were repoted in studies done by Singh et al[83],Charoo et al[84],Gandhi et al [80].Though the instruments used for LSCS were sterilised appropriately disparity in the outcome could be due to early rupture of membranes and contamination from environment during delivery.

BACTERIOLOGICAL PROFILE OF NEONATAL SEPTICEMIA:

In the present study, Candida species constituted the majority of isolates (69.56%) followed by bacterial isolates(30.44%). Studies conducted by Mane et

al[85],Pandita et al [86],Ballot et al[87], Basu et al [88] and kumar et al [89] also showed candida species as majority of isolates in suspected neonatal sepsis.

Mane et al[85] in their study at Nagpur, reported all their candida isolates to be candida albicans.However,on the contrary, Non albicans candida predominated in the studies done conducted by Roy et al[77],Vinod kumar et al[66],Desai et al[67],Gandhi et al[80] and Sharma et al[73].

Thus the recent reports suggest that candida albicans, which was responsible for nearly 80% of candidemia in the 1990's are being replaced by non albicans candida species in the present years.

Fungal sepsis is an important problem in sick new born infants, with the mortality rate between 21%-76%.definite diagnosis of fungal sepsis is difficult and pathogens msy take up time for isolation. Hence it would be prudent to treat babies with suspected fungal sepsis,with antifungal therapy, while awaiting culture results.emphirical antifungal therapy can be based on the knowledge of predominant fungal isolates from a particular unit.

The pathogens most often implicated to cause neonatal sepsis not only differ in geographical distribution but also change with respect to time even in the same area which can be attributed to the difference in living conditions according to Basavaraaj P et al[38].

Risk factors for fungal sepsis include low birth weight,gestational age <30 weeks,intravenous hyperalimentation,use of central catheters,mechanical ventilation and endotracheal intubation[90].

Fungal isolates being predominant were followed by bacterial isolates which constituted Klebsiella pneumoniae, Pseudomonas aeruginosa,Escherichia coli, Enterobacter cloacae,Staphylococcus epidermidis,Staphylococcus haemolyticus. Similar pattern of bacterial isolates were seen in studies done by Chacko et al[28],Desai et al[67],Vinodkumar et al[66],Rathod et al[91], and Gandhi et al[80].

Gram negative septicemia may be associated with meningitis,septic shock due to endotoxemia may be the presenting sign.these organisms may be acquired by the neonate during birth or on contact with colonized care givers,while in NIC. Environmental sources,such as ventilation systems and storage shelves have been implicated[92].

In the present study, CoNS constituted 8.70% of the total isolates.The CoNS that were isolated are Staphylococcus epidermidis and staphylococcus haemolyticus. Although CoNS are commensal organism with little pathogenicity in immunocompetent hosts,premature neonates are particularly susceptible to invasive infection. The first step in the pathogenicity of CoNS involves adherence of bacteria to the skin,mucosa, or indwelling artificial devices,commonly used in preterm neonates,Adherence is facilitated by a capsular polysaccharide adhesion consisting of poly-N-succinyl glucosamine.The ability of CoNS to produce slime and biofilms has been linked to increase virulence in the preterm neonates.

EVALUATION OF SCREENING TESTS :

Neonatal sepsis may present with non specific subtle symptoms and signs, which may intrigue even the most astute clinician. Definite diagnosis of neonatal septicemia depends on positive blood culture ,which takes around 48-72 hours.

Various haematological parameters have been utilised to screen for sepsis,with doubtful sensitivity and specificity. In the present study,limited parameters were evaluated in assisting the diagnosis of neonatal septicemia.These included PCT levels,CRP levels,Haemoglobin percentage,Total WBC counts and Platelet counts.Blood culture was being considered as a gold standard.

1. C-Reactive Protein Assay:

C- Reactive Protein acts as a scavenger causing opsonisation of bacteria and activation of the complement system thereby facilitating phagocytosis during inflammatory response. CRP assay, the most analysed parameter for years has higher likelihood of predicting sepsis among most other parameters.

In the present study,the sensitivity of CRP was 50% and the specificity was noted to be highest which was 92.30%. The positive and negative predictive values were found to be 92.30 % and 52.17 % respectively.

The table below shows the Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value done by different studies:

Sr.no	Author	Year of study	Place of study	Sensitivity	Specifity	Positive Predictive Value	Negative Predictive Value
1	Amposah et al [93]	2017	Ghana	50%	72.2%	37.5%	83.1%
2	Mohammed et al[59]	2015	Saudi Arabia	70%	60%	28%	80%
3	Sarala et al[94]	2016	Bangalore,India	50%	33.33%	31%	47.6%
4	Hasan et al[95]	2017	Mangalore, Karnataka	50%	52.9%	33.33%	100%
5	Aboud et al[62]	2010	Syria	80%	77%	77%	90%
6	Adib et al[61]	2012	Iran	45%	95%	30%	30%
7	Bollot et al[87]	2014	Korea	88.29%	58.17%	85.66%	13.2%
8	Ganeshan et al[96]	2016	Chennai,India	80%	65.7%	25%	95.83%
9	Suchitalingam et al[1]	2012	Tamilnadu ,India	55.6%	89.5%	58.8%	88.6%
10	Present study	2018	Belagavi, Karnataka	50%	92.30%	92.30%	52.17%

The differences in these studies may be due to the variation with respect to the timing of CRP assay after the clinical onset of infection in addition to the fact that all these studies measured CRP quantitatively with different cut-off points .

A sound clinical judgement combined with quantitative CRP assay could provide rational basis for the treatment decisions in the management of neonatal sepsis.such a strategy could probably reduce unnecessary antimicrobial therapy and the consequent emergence of resistant strains of the organisms.

Siddaiah et al[57] studies the role of CRP in deciding the duration of antibiotic therapy in neonatal sepsis and concluded that newborn with suspected sepsis having raised CRP levels needed a longer duration of antibiotic therapy of more than 7 days.

SERIAL LEVELS OF CRP:

Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection. Two CRP levels <1 mg/dL obtained 24 hours apart, 8 to 48 hours after presentation, indicate that bacterial infection is unlikely. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy. The positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infection.[97]

In the present study,there was persistent increase in the CRP seen in all the suspected and culture proven cases of neonatal sepsis which was done after 72 hours of antibiotic administration.This can be due to the various iatrogenic causes like IV Catheters, Endotracheal tube.

2. TOTAL WBC COUNTS

Total WBC counts showed the sensitivity of 61.11% and the specificity was found to be 53.84%. The positive predictive value and negative predictive values were 64.70% and 63.15% respectively.

Similar results were seen in other studies done by Das et al [98],Buch et al [99],Fazal et al[100],Dulhan et al[101],Panwar et al.[102]

Most of the studies concluded that though altered leucocyte count is a highly specific indicator, the sensitivity is very low in diagnosing sepsis.

The WBC count increases rapidly during the first few hours, leveling off thereafter. The result of WBC count can provide more information about the risk of sepsis after a few hours of birth.

Among neonates for whom a decision to start antibiotic can be deferred until after 4 hours of age, the WBC is more likely to be helpful. On the other hand, if neonates risk factors or symptoms are worrisome to draw a CBC and blood culture before 4 hours of age, it may be prudent to start antibiotics at the same time.

3. PLATELET COUNT:

Trombocytopenia is frequently encountered in critically ill neonates irrespective of age and maturity.

In the present study the sensitivity of platelet counts was 47.05% and specificity was 69.25%.positive predictive value was 66.66 % and negative predictive value was 37.5%.

The findings of our study are in concordance with prevalence of thrombocytopenia in most studies (30%-60%) suggesting that though reduced platelet counts was an important indicator in sepsis but it is not specific enough to be used as a sole marker [98–103].

In a study conducted by Buch et al 32.7% of culture proven sepsis had thrombocytopenia which is concordant with the present study (33.34%).[99]

There was no significant difference observed in the incidence of thrombocytopenia based on Gram positivity or negativity of the organism in this study

which is similar to a study done by Manzoni P et al [(104)] to assess organism specific response of platelet count in neonatal sepsis.

Analysis of both WBC and platelet counts have revealed that individual haematological findings should be interpreted with much caution since the haematological response may vary with gestational and post-natal age according to Ree et al[(105)] . These findings also vary with the time interval of the onset of sepsis and blood sampling . In addition, the influence of the site of sampling as the number of arterial and venous leukocytes are less than the capillary WBC values .

4. HAEMOGLOBIN PERCENTAGE:

Haemoglobin percentage was found to be a non-reliable indicator as it showed the least sensitivity compared to other markers.

5. PCT:

Like CRP, procalcitonin has been proposed as a marker for neonatal sepsis. The pro-inflammatory cytokines which play a key role in pathogenesis trigger the secretion of procalcitonin. In neonates elevated procalcitonin may help in predicting sepsis while lower levels rule out bacterial sepsis.

In the present study PCT levels were remarkably high among neonates with proven sepsis. This finding is comparable to the studies done by park et al [(106)] Zahedpasha et al[(65)].

Among the 36 neonates of suspected sepsis, PCT was elevated in 24 neonates whereas CRP was elevated in 13. Out of 23 culture proven sepsis elevated serum PCT was seen in 17 cases while elevated CRP was noticed in 12 cases. In our study the

sensisitivity and specificity of PCT was 69.56% and 53.84% when compared to that of CRP 50% and 92.30%.PCT showed the highest sensitivity and CRP showed highest specificity in the present study.Similar findings were reported by Sucilathangam G et al[1] also reported higher sensitivity of PCT and high specificity for CRP in detecting sepsis in correlation with CRP.

According to a study conducted by Ballot DE et al [107] though PCT could not be relied as a sole marker of sepsis, it plays a vital role in sepsis workup and with its high sensitivity and lower levels of PCT rules out sepsis.

The reliability of PCT in 28 neontes with early onset sepsis was studied by Chisea et al [94] and found that the sensitivity, specificity, PPV and NPV were 92.6%, 97.5%, 94.3% and 96.8% respectively. Though PCT was elevated in 24 of them at the time of presentation, significant rise in CRP levels were seen in only half of them with elevated PCT. Most of the studies including those of Rathod et al [91] and abdalla et al (108)emphasized the investigative role of PCT in diagnosing neonatal sepsis rather than CRP and concluded that PCT was more sensitive compared to CRP which correlates with our study.

The sensitivity of CRP is negated during the initial 48 hours of infection since there is only a slow rise. Further elevated CRP concentrations in conditions other than sepsis like PROM and meconium aspiration are found to affect its specificity as well.

In this study, the sepsis indicators which were analysed and correlated with blood culture showed haemoglobin percentage has a marked specificity , it showed lowest sensitivity among all the sepsis markers analysed .Total WBC counts showed second highest sensitivity and the least Negative Predictive Value compared to all

other markers of sepsis. Thrombocytopenia and haemoglobin percentage was found to be a non-specific indicator compared to other markers. PCT showed the highest sensitivity followed by total WBC counts and CRP. CRP showed highest specificity and positive predictive value among all other markers.

Hence Procalcitonin can be used as a sensitive tool in diagnosing sepsis. It can be used to differentiate bacterial from viral infections as it is specific for bacterial and fungal sepsis. Also it assists in diagnosing sepsis early on the day of admission itself and also prevents inadvertent use of antibiotics thereby reducing further emergence of drug resistant strains.

Inspite of its essential role in sepsis, with all the added advantages Procalcitonin still cannot be relied as a sole marker. Combination of Total WBC counts, C-Reactive Protein and Procalcitonin levels is recommended as it shows an increase in its sensitivity and specifity in early diagnosis of Neonatal sepsis.

CONCLUSIONS:

In the present study, the risk factors commonly associated with neonatal sepsis were found to be Prematuriy, Low Birth Weight, LSCS, premature/prolonged rupture of membranes. Early Onset Sepsis was more common than Late Onset Sepsis. Candida sepsis was predominantly seen among all the culture isolates.

The sepsis indicators which were analysed and correlated with blood culture.

Procalcitonin showed the highest sensitivity followed by Total WBC counts and C-Reactive Protein.C-Reactive Protein showed highest specificity and positive predictive value among all other markers. Procalcitonin was found to be a sensitive tool for early diagnosis whereas C-Reactive Protein and Total WBC counts for predicting the outcome of sepsis when compared to other markers.

Procalcitonin can be used as a sensitive tool in diagnosing sepsis. It can be used to differentiate bacterial and fungal from viral infections as it is specific for bacterial and fungal sepsis. Also it assists in diagnosing sepsis early on the day of admission itself and prevents inadvertent use of antibiotics thereby reducing further emergence of drug resistant strains.

Haemoglobin percentage and platelet counts showed the least sensitivity.

But neither of these markers are 100% sensitive nor 100% specific to be relied as a sole marker. We would like to conclude that blood culture even though considered as gold standard it is time consuming and at times gives false negative results. The greatest predictability can be achieved by the combination of total WBC counts,CRP and PCT rather than a single biomarker. So it is high time to initiate

rigorous steps to expand the continuing search for a definitive diagnostic biomarker using multi-centric studies based on a harmonized protocol.

Candida species being majority of isolates in the present study, Preventive measures such as use of filters for Total Perenteral Nutrition, prophylactic antifungal use, and a restrictive policy of antibiotic to decrease Candida colonization infection rates should be implemented ,which decreases mortality and morbidity associated with these infections.

Also, previously ignored, Non Albicans Candida species especially *Candida glabrata* received little attention.Therefore, surprisingly our knowledge regarding them is not only incomplete, but also significantly lacking. we now need to have more studies and more tools, specially molecular tools to study the epidemiology of this emerging problem.

A much detailed intervention and multiple large scale cross sectional studies with a much higher sample size should be performed to further confirm these findings and to make combination of C-Reactive Protein, Procalcitonin and Total WBC counts as the “Early diagnostic markers” of sepsis. Until then the isolation of the causative organism by culture occupies the centre stage in diagnosing sepsis.

SUMMARY:

- In this study 36 neonates with signs suggestive of sepsis were admitted to NICU of Dr.Prabhakar Kore Hospital, Belagavi over a period of 1 year from January 2017 to December 2017.
- Culture proven sepsis was seen in 63.88% of all the suspected neonates with sepsis.
- 63.89% male neonates and 36.11% female neonates were included in the study.
- Early onset sepsis was seen in all the 36 neonates with suspected sepsis. There were no cases of late onset sepsis recorded during this study period.
- Culture positivity was significantly high in preterm neonates 95.65% compared to term neonates 4.35%
- Significant increase in culture proven sepsis was noted among neonates of low birth weight than those with normal birth weight.
- In this study there was no significant difference in rate of culture isolation among the neonates based on parity of the mother.
- The incidence of culture proven sepsis was significantly high among neonates delivered by LSCS (82.60%) in comparison with those delivered by NVD (17.39%). A four fold rise in culture positivity was noticed among the neonates delivered by LSCS.
- Maternal risk factors predisposing neonates to sepsis included highest number of cases had premature/prolonged rupture of membrane 21.74% followed by preclamsia 17.40%,prolonged labour 4.35% and maternal pyrexia 4.35%.

Other risk factors included twin pregnancy, Invitro conception, Gestational diabetes mellitus, Cervical stitch insitu, cervical encirclage etc.

- Fungal isolates constituted majority of isolates in the present study 69.44% followed by bacterial isolates 30.44%.There was a two fold rise in fungal isolates compared to bacterial isolates in the present study.
- Among the fungal isolates, candida glabrata 34.78% constituted majority of isolates followed by candida tropicalis 30.43% and candida cruzi 4.35%. Among the bacterial isolates klebsiella pneumonia constituted majority of isolates 8.09% followed by pseudomonas aeruginosa 4.35%,Escherichia coli 4.35%,enterobacter cloacae 4.35%,staphylococcus epidermidis 4.35%, staphylococcus haemolyticus 4.35%.
- Candida glabrata was the commonest causative agent in all the early onset sepsis cases.
- The screening tests applied in the present study showed the following results:

a) PCT: Sensitivity-65.59%
Specificity-53.84%
Positive Predictive Value-72.72%
Negative Predictive Value-50%

b) 1^{ST} CRP: Sensitivity-50%
Specificity-92.30%
Positive Predictive Value-92.30%
Negative Predictive Value-52.17%

c) Haemoglobin percentage: Sensitivity-26.06%
Specificity-84.16%
Positive Predictive Value-75%

Negative Predictive Value-39.28%

d) Total WBC counts : Sensitivity-61.11%

Specificity-53.84%

Positive Predictive Value-64.70%

Negative Predictive Value- 36.84%

e)Platelet counts : Sensitivity-47.05%

Specificity-69.25%

Positive Predictive Value-66.66%

Negative Predictive Value-37.5%

- Though haemoglobin percentage has a marked specificity , it showed lowest sensitivity among all the sepsis markers analysed in this study .
- Total WBC counts showed second highest sensitivity and the least Negative Predictive Value compared to all other markers of sepsis.
- Thrombocytopenia and haemoglobin percentage was found to be a non-specific indicator compared to other markers.
- PCT showed the highest sensitivity followed by total WBC counts and CRP. CRP showed highest specificity and positive predictive value among all other markers which were correlated with blood culture in this study.
- Inspite if antibiotics administration, there was persistent rise in CRP seen in all the culture proven sepsis cases which was repeated after 72 hours of antibiotic administration.
- In the present study ,Serum PCT levels ,serum CRP levels and total WBC counts were more reliable markers compared to others in the context of early diagnosis of neonatal sepsis and combination of these three markers increase the predictability of sepsis rather than a single biomarker.

APPENDIX

Gram stain Procedure: Hucker's modification

Principle: After treatment with decolorizing agents, gram positive bacteria retain para- rosaniline dyes and appear violet colorwhile gram negative bacteria lose the dye and take up counter stain and appear pink in color.

Procedure:

a) A clean grease free glass slide was labelled and a thin smear was made on it using the first high vaginal swab and allowed to air dry.

b) The smear was fixed by passing the slide three to four times through the flame of a Bunsen burner.

c) Slide was then placed on the slide rack and the smear overlaid with crystal violet solution.

d) After 20 seconds, the slide was washed thoroughly with tap water.

e) Subsequently, the smear was overlaid with Gram iodine solution for 20 seconds and washed again with water.

f) The smear was held between the thumb and fore finger and the surface flooded with a few drops of acetone-alcohol decolorizer, until no color washed off.

g) The smear was washed with running water and placed back on the staining rack. Surface of the smear was overlaid with safranin (counter stain) for 10 seconds and washed with running water.

h) The slide was placed in an upright position in a rack, allowing excess water to drain off.

i) The stained smear, after being dried was examined under 100 X (oil) immersion objective lens.

Quality control: Gram positive: *Staphylococcus aureus* ATCC 25923

Gram negative: *Escherichia coli* ATCC 25922

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ANNEXURES

ANNEXURE I : ETHICAL CLEARANCE CETIFICATE

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 07 **Date: 17/10/2016**

To,

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFECTIVENESS OF SERUM PROCALCITONIN AND SERIAL LEVELS OF C-REACTIVE PROTEIN VERSUS BLOOD CULTURE IN EARLY DIAGNOSIS OF NEONATAL SEPSIS"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

5

ANNEXURE I : CONSENT (ENGLISH,KANNADA AND HINDI)

CONSENT FOR PARTICIPATION IN RESEARCH

TITLE: " EFFECTIVENESS OF SERUM PROCALCITONIN AND SERIAL LEVELS OF C-REACTIVE PROTEIN VERSUS BLOOD CULTURE IN EARLY DIAGNOSIS OF NEONATAL SEPSIS".

Study Investigator

Guide

Co-guide

INTRODUCTION:

- Neonatal infection is an important cause of sickness in neonates,which needs admission and treatment in NICU.
- Rapid and correct diagnosis of neonatal sepsis is often difficult in routine clinical practice because the signs and symtoms of this condition can be similar to other non infectious condition.
- Blood cultures(i.e to grow bacteria from blood sample) help in the identification of serious bacterial infections, but may give false negative results, particularly after maternal antibiotic use and might also result in false positive results because of difficulty in specimen contamination
- Serum Procalcitonin and C-Reactive proteins are two important tests that have been found to be useful in correct diagnosis of infection in newborns. Correct diagnosis will help to administer correct antibiotics early and thus prevent complications of infection and unnecessary use of antibiotics.

OBJECTIVE OF THE STUDY: To compare the diagnostic performance of serum Procalcitonin and serum C-Reactive Protein to that of Blood culture and Haematological parameters in early diagnosis of Neonatal sepsis.

PROCEDURE INVOLVED:

You are requested to participate in this study which will help to provide appropriate and effective treatment. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge

If you agree to be a part of this study, extra blood sample will be collected for serum procalcitonin while collecting sample for routine sepsis workup. .

RISKS AND BENEFITS:

There are no risks involved and benefit is to know the serum procalcitonin and c-reactive protein levels as early diagnostic markers in a case neonatal septicemia.

ALTERNATIVES:

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with Jawaharlal Nehru Medical College. If you decide to participate you are free to withdraw at any time.

PRIVACY AND CONFIDENTIALITY: The only people to know that you are a research subject are members of the research team. No information about you or provided by you during research will be disclosed to others without your written permission, exceptin emergency to protect your rights and welfare.

AUTHORIZATION TO PUBLISH RESULTS:

When the results of research are published or discussed in a conference, no information will be displaced that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION:

You will not be paid /offered any gifts/incentives for participating in the study. You will not be reimbursed for expenses.

In case you have any questions related to the study, you can contact the study investigator,

Dr.Pragati Narayanakar (mobile no. 9686132836), Dr. (Mrs.)S.C.Metgud (mobile no.

In case you have any questions about your rights as a participant, you can contact Dr.Ganga S Pilli, Professor of Pathology and Chairman of Institutional Ethics Committee, JNMC (mob:9480275601)

CONSENT STATEMENT

I, the undersigned _____ have been explained in my vernacular language about the study and my participation in the study is voluntary. If I want, I can withdraw at any time. Also I have been given enough time to clear my doubts and rights as study participant.

Signature or left hand thumb print of participant or legally authorized representative.

Participant's Name

Witness Name signature

Experimenter's Name signature

Date:

Place:

ಕೆ.ಎಲ್.ಇ ವಿಶ್ವವಿದ್ಯಾಲಯ
ಜವಹರಲಾಲ ನೆಹರು ವೈದ್ಯಕೀಯ ಮಹಾವಿದ್ಯಾಲಯ, ಬೆಳಗಾವಿ
ಸೂಕ್ಷಜೀವ ವೈದ್ಯಕೀಯ ವಿಭಾಗ

"ಪ್ರಿಕ್ಯಾಲ್ಸಿಟೊನಿನ್ ರಕ್ತಸಾರ ಮತ್ತು ಸಿ-ರಿಯಾಕ್ಟಿವ್ ಪ್ರೊಟೀನ್ ರಕ್ತಸಾರಗಳ ಕ್ರಮಬದ್ಧ ಮಟ್ಟಗಳ ವಿರುದ್ದರಕ್ತ ಸಂಸ್ಕೃತಿ - ನವಜಾತಶಿಶುಗಳಲ್ಲಿ ನಂಜಿನಆರಂಭಿಕ ರೋಗನಿರ್ಣಯಗಳು"

ಪರಿಚಯ:

ನವಜಾತಶಿಶುಗಳಲ್ಲಿ ಖಾಯಿಲೆಗಳ ಪ್ರಮುಖಕಾರಣ ನಂಜುಅಥವಾ ಸೋಂಕು, ಇದಕ್ಕಾಗಿ ನವಜಾತತೀವ್ರ ಶುಶ್ರೂಷೆಘಟದಲ್ಲಿಅಂಗೀಕಾರ ಮತ್ತುಚಿಕಿತ್ಸೆಅಗತ್ಯ.

ನವಜಾತಶಿಶುಗಳ ನಂಜಿನ ಶೀಗ್ರವಾದ ಮತ್ತು ನಿಖರವಾದ ನಿರ್ಣಯ ತರಗರದುಕೊಳ್ಳುವುದು ಕಠಿಣವಿಕರಂದರೆ ರೋಗಲಕ್ಷಣಗಳು ಬೇರೆ ಸಾಂಕ್ರಾಮಿಕ ರೋಗಲಕ್ಷಣಗಳಂತೆ ಕಂಡುಬರಿತ್ತವೆ.

ತೀರ್ವವಾದ ಅಣುಜೀವಿಗಳ ಸೋಂಕನ್ನು ಪತ್ತೆ ಹಚ್ಚುವುದರಲ್ಲಿರಕ್ತ ಸಂಸ್ಕೃತಿಉಪಯೋಗಕರವಾದದ್ದು, ಆದರೆ ರೋಗನಿರೋದಕಗಳ ಬಳಕೆಗಳನಂತರ ತಪ್ಪುಪರಿಣಾಮಗಳು ಲಭ್ಯವಾಗಬಹುದು. ನವಜಾತಶಿಶುಗಳ ಸೋಂಕಿನ ರೋಗಗಳನ್ನು ಪತ್ತೆ ಹಚ್ಚುವುದರಲ್ಲಿ ಪ್ರಿಕ್ಯಾಲ್ಸಿಟೊನಿನ್ರಕ್ತಸಾರ ಮತ್ತು ಸಿ-ರಿಯಾಕ್ಟಿವ್ ಪ್ರೊಟೀನ್ರಕ್ತಸಾರ ಮಹತ್ತರ ಪಾತ್ರ ನಿರ್ವಹಿಸುತ್ತದೆ.

ಅಧ್ಯಯನದಉದ್ದೇಶ:

ನವಜಾತಶಿಶುಗಳಲ್ಲಿ ನಂಜಿನಆರಂಭಿಕ ರೋಗನಿರ್ಣಯಗಳನ್ನಯ ಪತ್ತೆ ಹಚ್ಚುವುದರಲ್ಲಿ ಪ್ರಿಕ್ಯಾಲ್ಸಿಟೊನಿನ್ ರಕ್ತಸಾರ ಮತ್ತು ಸಿ-ರಿಯಾಕ್ಟಿವ್ ಪ್ರೊಟೀನ್ ರಕ್ತಸಾರ ವರುದ್ದರಕ್ತ ಸಂಸ್ಕೃತಿ ಮತ್ತು ಇತರೆ ರಕ್ತಸಂಭಂದಿತ ಪರೀಕ್ಷಗಳ ನಡುವೆ ಹೋಲಿಕೆ.

ವಿಧಾನ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಕೆಲವು ಪ್ರಶ್ನೆಗಳಿಗೆ ಉತ್ತರ ನೀಡಬೇಕು. ಈ ಕಾರ್ಯವಿಧಾನ 20 ರಿಂದ 30 ನಿಮಿಶಗಳ ಕಾಲ ತೆಗೆದುಕೊಳ್ಳಬಹುದು. ನೀವು ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದಲ್ಲಿ ನಿಮ್ಮ ಮಗುವಿನ ರಕ್ತ ಮಾದರಿಯನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು.

ಪ್ರಯೋಜನಗಳು:

ಈ ಅಧ್ಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಂದ ನಿಮಗೆ ಯಾವುದೇರೀತಿಯ ನೇರ ಲಾಭಇರುವುದಿಲ್ಲ ಮತ್ತು ಸಂಶೋಧಕರುಯಾವುದೇರೀತಿಯಆಶ್ವಾಸನೆಯನ್ನು ನೀಡುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನ ಸಮಾಜದ ಹಿತಾಸಕ್ತಿಗಾಗಿ ಬಳಸಲಾಗುವುದು.

ಸಂಭವನೀಯ ಅಪಾಯಗಳು:

ಅಧ್ಯಯನ ಮಾಡುವಅನ್ವಯಿಸಬಹುದಾದ ವಿಧಾನಗಳು ಸುರಕ್ಷಿತವಾಗಿರುತ್ತವೆ. ಅಧ್ಯಯನದಂದ ಯಾವುದೇ ಅಪಾಯವಿಲ್ಲ.

ಭಾಗವಹಿಸುವಿಕೆಯ ವೆಚ್ಚ:

ಅಧ್ಯಯನ ವೆಚ್ಚ ಸಂಶೋಧಕ ಸಂಪೂರ್ಣವಾಗಿ ಭರಿಸುತ್ತಾನೆ. ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಗೆ ನೀವು ಯಾವುದೆ ವೆಚ್ಚ ಭರಿಸಬೇಕಾವಿರುವುದಿಲ್ಲ.

ಕಾನೂನಿನ ಹಕ್ಕುಗಳು:

ಈ ಸಮ್ಮತಿ ನಮೂನೆಯ ಸಹಿ ಮೂಲಕವಾಗಿ ನಿಮ್ಮ ಹಕ್ಕುಗಳನ್ನು ಬಿಟ್ಟುಕೊಡುವುದಿಲ್ಲ.

ಗೌಪ್ಯತೆ ಮತ್ತುರಹಸ್ಯತೆ:

ನಿಮ್ಮ ವೈಯಕ್ತಿಕ ಗುರುತನ್ನು ತೋರಿಸಲಾಗುವುದಿಲ್ಲ. ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಸಂಯೇತಿಸಿ ಇಡಲಾಗುತ್ತದೆ. ಮಾಹಿತಿಯನ್ನು ಸಂಶೋಧಕನಿಗೆ ಬಿಟ್ಟು ಬೇರೆಯಾರಿಗು ನಿಮ್ಮಗುರುತನ್ನು ತೋರೊಸಲಾಗುವುದಿಲ್ಲ ಮತ್ತು ರಹಸ್ಯವಾಗಿ ಇಡಲಾಗುವುದು.

ಅಧ್ಯಯನ ಹಿಂಪಡೆಯುವಿಕೆ:

ನೀವು ಯಾವುದೆ ಸಮಯದಲ್ಲಿ ನಿಮ್ಮ ಮಾಲನ್ನು ಬಯಸದಲ್ಲಿ ಯಾವುದೆಕಾರಣ ವಿಲ್ಲದೆ ಹಿಂಪಡೆಯ ಬಹುದಾಗಿದೆ.

ಅಧಿಕೃತವಾಗಿ ಫಲಿತಾಂಶಗಳ ಪ್ರಕಟಣ:

ಸಂಶೋಧಕ ಈ ಅಧ್ಯನದಿಂದ ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ವೈಜ್ಞಾನಿಕ ನಿಯತಕಾಲಿಕಗಳಲ್ಲಿ, ಸಮಾವೇಶಗಳಲ್ಲಿ ಮಂಡನೆಗೆ ಬಳಸಬಹುದು. ಅದಾಗ್ಯೂ ನಿಮ್ಮ ವೈಯಕ್ತಿಕ ಗುರುತನ್ನು ತೋರಿಸಲಾಗುವುದಿಲ್ಲ.

ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಗೆ ಪ್ರೋತ್ಸಾಹಧನ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಗೆ ಯಾವುದೇರೀತಿಯ ಪ್ರೋತ್ಸಾಹಧನ ನೀಡಲಾಗುವುದಿಲ್ಲ.

ಪ್ರಶ್ನೆಗಳು:

ನೀವು ಅಧ್ಯಯನದ ಬಗೆ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳನ್ನು ಹೊಂದಿದ್ದರೆ **ಡಾ. ಪ್ರಗತಿ**

ಹೊಂದಿದ್ದರೆ**ಡಾ. (ಶ್ರೀಮತಿ) ಗಂಗಾ. ಎಸ್. ಪಿಳ್ಳಿ,** ಕಾರ್ಯಾಧ್ಯಕ್ಷರು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮೀತಿ, ಮಾನವನ ಸಂಶೋಧನ ವಿಭಾಗ, ಜೆ.ಎನ್.ಎಂ.ಸಿ. ಬೆಳಗಾವಿ–590010, ಸಂಚಾರಿವಾಣಿ ಸಂಖ್ಯೆ: 9480275601 ಅಥವಾ **ಡಾ. (ಶ್ರೀಮತಿ) ಎನ್. ಎಸ್. ಮಹಾಂತ ಶೆಟ್ಟಿ,** ಪ್ರಾರ್ಚಾಯಕರು, ಜೆ.ಎನ್.ಎಂ.ಸಿ. ಬೆಳಗಾವಿ–590010, ಸಂಚಾರಿವಾಣಿ ಸಂಖ್ಯೆ: 0831–2471350 ಇವರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು.

ಒಪ್ಪಿಗೆಯನ್ನು ಸೂಚಿಸುವ ಪತ್ರ

ಈ ಸಮ್ಮತಿ ನಮೂನೆಯಲ್ಲಿರುವಎಲ್ಲಾ ವಿಶಯಗಳನ್ನು ನನ್ನ ಸ್ಥಳೀಯ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ. ನನ್ನ ಗಮನಕ್ಕೆ ಬಂದಂತಅಧ್ಯಯನದಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳನ್ನು ಉತ್ತರಿಸಿದ್ದಾರೆ ಮತ್ತು ಸ್ಪಷ್ಟ ಪಡಿಸಿದ್ದಾರೆ. ಇದಲ್ಲದೆ ನಾನು ಅಧ್ಯಯನದಯಾವುದೇ ಹಂತದಲ್ಲಿ ಈ ಸಮ್ಮತಿಯನ್ನು ಹಿಂದೆ ಪಡೆಯುವ ಸಂಪೂರ್ಣ ಹಕ್ಕು ಇದೆಎಂದು ತಿಳಿಸಿದ್ದಾರೆ. ನಾನು ನೀಡಿರುವ ಮಾಹಿತಿಯನ್ನುರಹಸ್ಯವಾಗಿಡುವುದಾಗಿಯೂ ಮತ್ತು ಕೇವಲ ಸಂಶೋಧನೆಯಉದ್ದೇಶಕ್ಕೆ ಬಳಸಲಾಗುವುದೆಂದು ಹೇಳಿದ್ದಾರೆ. ನನ್ನ ವ್ಯಯಕ್ತಿಕಗುರುತನ್ನು ಬಹಿರಂಗ ಪಡಿಸಲಾಗುವುದಿಲ್ಲ ಎಂದುಆಶ್ವಾಸನೆಯನ್ನು ನೀಡಿದ್ದಾರೆ.

ನಾನು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನನ್ನ ಸ್ವಯಂ ಪ್ರೇರಿತಎಪ್ಪಿಗೆ ನೀಡಿರುತ್ತೇನೆ. ನಾನು ಗುರುತು ಹಿಡಿಯುವಇವರ ಮುಂದೆ ಪ್ರತ್ಯಕ್ಷವಾಗಿಒಪ್ಪಿಗೆ ಸೂಚಿಸಿ ನಮೂನೆಗೆ ಸಹಿ ಮಾಡಿದ್ದೆನೆ.

ಭಾಗವಹಿಸಿದವರ ಹೆಸರು ಮತ್ತು ಸಹಿ / ಎಡಹೆಬ್ಬೆಟ್ಟಿನಗುರುತು

ಸಾಕ್ಷಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ / ಎಡಹೆಬ್ಬೆಟ್ಟಿನಗುರುತು

ಸಂದರ್ಶಕರ ಹೆಸರು ಮತ್ತು ಸಹಿ

ದಿನಾಂಕ:
ಸ್ಥಳ:

के.एल.युनव्हर्सिटी
जवाहरलाल नेहरु वैद्यकिय महाविद्यालय बेळगांवी
समुदाय वैद्यकिय विभाग

प्री. कॅल्सीटोनिंन् रक्तसार-आणि सी. रिअॅक्टीव प्रोटीन रक्तसारांच्या क्रमबध्द मटांच्या विरुध्द रक्त संस्कृति-नवजात शिशुमध्ये सेप्टीक आरंभिक रोग निर्णय

संशोधक डॉ. प्रगती नारायणकर

परि- [illegible] सेप्टीक अथवा इन्फेक्षन या करिता नवजात शिशु तीव्र शुश्रुषा घटकात अंगीकार करणे आणि चिकित्सा अगत्य अवश्य.

नवजात शिशुंच्या सेप्टीक शिघ्र आणि निश्चय निर्णय घेणे कठीण आहे म्हणजे रोग लक्षण वेगळे वेगळे सांक्रमिक रोग सारखं दिसून येतात.

तीव्र अनुजीवी इन्फेक्शन पत्ता करण्याकरिता रक्त संस्कृती उपयोग आहे. पण रोग निरोधक उपयोगानंतर चूकीचा परिणाम मिळेल नवजात शिशुंच्या इन्फेक्शन शोधते वेळी पत्ता करण्या प्री. कॅल्सीटोनिंन् रक्तसार-आणि सी. रिअॅक्टीव प्रोटीन रक्तसार महत्वाचा पात्र आहे.

अध्ययनाचे उद्देश:

नवजात शिशुमध्ये सेप्टीक सुरुवात प्रारंभिक रोग निर्णयवर शोध लावण्यात प्री. कॅल्सीटोनिंन् रक्तसार-आणि सी. रिअॅक्टीव प्रोटीन, रक्तसारांच्या क्रमबध्द मटांच्या विरुध्द रक्त संस्कृति आणि इतर रक्त संबंधी परिक्षामध्ये साम्यता.

विधान :

या अध्ययनात तुम्ही तुमच्या सामाजिक विवर आहार आणि संस्कृतिक परिपाठ आहार सुरक्षितता आणि आहारापासून होणारे अनारोग्यांच्यां काही प्रश्नाला उत्तर देणे. तुमचे ज्ञान वर्तने आणि आहार सुरक्षता क्रम सांगणे हा कार्यक्रम २०-३० निमिष कालावधीत घेण्यात येईल. तुम्ही संमती दिल्यानंतर तुमच्या शिशुच्या रक्ताचा नमुना घेण्यात येईल.

प्रयोजने :

या अध्ययनामध्ये भाग घेतलेल्यांना कुठलाही लाभ नाही. आणि संशोधक सहीत कुठल्याही रितिचा आश्वासन देत नाही. हे अध्ययन समाजाच्या हितासाठी उपयोग करता येईल.

संभवनीय अपाय :

अध्ययन करिता करण्यात येणारे विधान सुरक्षित आहे. आणि या अध्ययनापासून कुठलाही अपाय नाही.

भाग घेण्यासाठी खर्च :

अध्ययनाकरिता खर्च संशोधक संपूर्ण भरतात. तुम्ही भाग घेण्याकरिता कुठलाही खर्च द्यायची आवश्यकता नाही.

कायद्यांचे हक्क :

या सम्मती फार्म सही केल्याबद्दल तुम्ही कुठलाही हक्क सोडून दिलेला नाही.

गोपनियता व रहस्य :

तुमच्या वैयक्तिक ओळख दाखवित नाही. संग्रह केलेले सर्व माहिती संरक्षण करता येईल. आणि ते माहिती संशोधकाला सोडून दुसऱ्या कुणालापण तुमची ओळख दाखवता येत नाही. आणि रहस्य ठेवण्यात येईल.

अध्ययन मागे घेण्यासाठी :

तुम्ही कुठल्याही वेळामध्ये तुमचे माल अपेक्षा केल्यास कारण न देता मागे घेण्यात येईल.

अधिकृत फलतांश जाहिर करणे:

संशोधक या अध्ययनामध्ये संग्रह केलेली माहिती वैज्ञानिक डेली पेपर समावेश मध्ये ठेवण्यात येईल. पण तुमचे वैयक्तिक ओळख दाखवित नाही.

या अध्ययनात भाग घेतलेल्यांना कुठलेही प्रोत्साहन देण्यात येणार नाही.

प्रश्ने :

[illegible] प्रश्न विचारणार असाल तर डॉ. **प्रगती**

तुम्ही संशोधनात भाग घेऊन हक्काकरता कुठलाही प्रश्न विचारणार असाल तर, डॉ. (श्रीमती) गंगा एस. पिल्ली, कार्याध्यक्ष संस्थिक नैतिक समिती, मानव संशोधन विभाग, जे.एन.एम.सी, बेळगावी ५९००१०. फोन नं. ०८३१- २४७१७०१ अथवा डॉ. श्रीमती एन.एस. महांतशेट्टी प्राचार्य जे.एन.एम.सी, बेळगावी ५९००१०. मोबाईल नं. ०८३१-२४७१३५० यांना संपर्क करणे.

सम्मति सुचविलेले पत्र

या फार्म मध्ये असलेले सर्व विषय मला माझी भाषामध्ये सांगितलेले आहे. मला संशय लेले सर्व अध्ययनाच्या प्रश्नांचे उतर दिलेले आहे आणि स्पष्ट केलेले आहे. याशिवाय ध्ययनाच्या कुठल्याही अंतामध्ये या सम्मतीपत्र मागे घेण्याचे संपूर्ण हक्क मला आहेत. म्हणून लिखितेले आहे. आणि मी दिलेली माहिती रहस्य ठेवण्याबद्दल आणि ती माहिती फक्त संशोधनासाठी उपयोग करता येईल असे सांगितलेले आहे. माझ्या वैयक्तिक माहिती, ओळख ोर करत नाही असे आश्वासन केलेले आहे.

मी या अध्ययनामध्ये भाग घेण्याकरिता स्वयं सम्मती दिलेली आहे. आणि माझी ओळख लगाऱ्यांना त्याचेपुढे सम्मति देवून सही केलेली आहे.

भाग घेतलेल्यांची नांवे व सही/ डाव्या हाताचा अंगठाचे निशाण

शोधकाचे नांव व सही/ डाव्या हाताचा अंगठाचे निशाण

साक्षीदारांचे नांव व सही:

ठिकाण :
दिनांक :

ANNEXTURE III :PROFORMA

QUESTIONNAIRE (PROFORMA) USED FOR COLLECTING THE DATA

1. Name of patient: B\O

2.IP no:

3. Pt no:

4.Inborn/Outborn:

5. Sex:

6. Date of Birth:

7. Date of admission:

8. Date of discharge:

9. Admission age:

10. Admission Weight:

11.Diagnosis:

12. Mode of Delivery:

13.Indication of Delivery:

14. Maternal data: **Obstretic Score:** **Blood group:**

15.Obstretric history:

16.Maternal risk factors:

17.Neonatal risk factors:

18.Hb percent%:

19.WBC count:

20.Platelet count:

21. CRP before Antibiotics administration: Date- Report-

22. CRP after 72 hours of Antibiotics administration: Date- Report-

23.Serum Procalcitonin: Date- Report-

24.Blood culture: Date- Report-

25.Remarks:

ANNEXTURE IV: SERUM PROCALCITONIN KIT LITERATURE

Elecsys BRAHMS PCT

cobas®

Procalcitonin

REF **05056888** 200 100

For USA: Elecsys BRAHMS PCT

05056888200 V 11
http://e-labdoc.roche.com

English

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

For USA: For prescription use only.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

2-methyl-2H-isothiazol-3-one hydrochloride

EUH 208 May produce an allergic reaction.

Product safety labeling primarily follows EU GHS guidance.

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Method Sheet download

The box at the top of this document shows the product code together with the respective document version.
Please go to http://e-labdoc.roche.com to download this document.
The website displays either the version listed here or, if available, any later version that is also valid for this product code. If you have no internet access, please contact your local Roche affiliate to obtain the document free of charge.

US Users

05056888200
https://usdiagnostics.roche.com

In case of problems, please contact US Technical Support (1-800-428-2336) to obtain the document.

Deutsch

Vorsichtsmaßnahmen und Warnhinweise

In-vitro-Diagnostikum.
Die beim Umgang mit Laborreagenzien üblichen Vorsichtsmaßnahmen beachten.
Die Entsorgung aller Abfälle ist gemäß den lokalen Richtlinien durchzuführen.
Sicherheitsdatenblatt auf Anfrage für berufsmäßige Benutzer erhältlich.

Für USA: "For prescription use only."

Die Packung enthält Bestandteile, die gemäß der Verordnung (EG) Nr. 1272/2008 wie folgt klassifiziert sind:

2-Methyl-2H-isothiazol-3-on Hydrochlorid

EUH 208 Kann allergische Reaktionen hervorrufen.

Die Produktsicherheitskennzeichnung folgt in erster Linie den in der EU gültigen GHS-Regularien.

Humanmaterial gilt als potentiell infektiös. Für alle aus Humanblut hergestellten Produkte wird nur Blut von einzeln getesteten Spendern verwendet, bei denen weder Antikörper gegen HCV und HIV noch HBsAg nachzuweisen sind. Die angewendeten Testmethoden sind von der US-Gesundheitsbehörde (FDA) genehmigt bzw. erfüllen die Anforderungen der Europäischen Direktive 98/79/EG, Anhang II, Liste A.

Da keine Testmethode mit absoluter Sicherheit eine potentielle Infektionsgefahr ausschließen kann, sollte das Material mit der gleichen Sorgfalt behandelt werden wie eine Patientenprobe. Im Falle einer Exposition ist entsprechend den Anweisungen der zuständigen Gesundheitsbehörden vorzugehen.

Schaumbildung bei allen Reagenzien und Probenarten (Proben, Kalibratoren und Kontrollen) vermeiden.

Download von Merkblättern

Der eingerahmte Text am Beginn des Dokumentes zeigt den Produkt-Code sowie die dazugehörige Version des Dokumentes.
Dieses Dokument kann von der folgenden Webseite heruntergeladen werden:
http://e-labdoc.roche.com.
Die Webseite zeigt die hier referenzierte Version oder aber, falls bereits verfügbar, eine ebenfalls für diesen Produkt-Code gültige höhere Version.
Sollten Sie keinen Internetzugang haben, erhalten Sie bei Ihrer Roche-Vertretung das Dokument kostenlos.

Français

Précautions d'emploi et mises en garde

Pour diagnostic in vitro.
Observer les précautions habituelles de manipulation en laboratoire.
L'élimination de tous les déchets doit être effectuée conformément aux dispositions légales.
Fiche de données de sécurité disponible sur demande pour les professionnels.

Pour les USA: Usage uniquement sur prescription.

Ce coffret contient des substances classées de la manière suivante selon le règlement CE 1272/2008:

2-méthyl-2H-isothiazol-3-one, chlorhydrate

EUH 208 Peut produire une réaction allergique.

L'étiquetage de sécurité du produit est principalement conforme à la réglementation CLP/GHS.

Tous les matériaux d'origine humaine doivent être considérés comme potentiellement infectieux. Tous les dérivés de sang humain utilisés ont été préparés uniquement à partir de sang de donneurs où la recherche de l'antigène HBs et des anticorps anti-VHC et anti-VIH a conduit à un résultat négatif. Les méthodes utilisées pour le dépistage étaient approuvées par la FDA ou conformes à la directive européenne 98/79/CE, Annexe II, liste A.

Cependant, comme le risque d'infection ne peut être exclu avec certitude par aucune méthode, ce produit doit être traité avec le même soin que les échantillons de patients. En cas d'exposition, suivre les directives de l'autorité compétente en matière de santé.

Éviter la formation de mousse dans les réactifs et les échantillons de tous types (échantillons de patients, calibrateurs et contrôles).

Téléchargement de fiches techniques

Le cadre en haut de la page montre le code du produit et la version du document.
Ce document est téléchargeable sur http://e-labdoc.roche.com.
Le site affiche la version indiquée ci-dessus ou toute autre version ultérieure disponible correspondant au code du produit. Si vous n'avez pas accès à Internet, veuillez contacter le représentant Roche de votre pays. Vous obtiendrez ce document gratuitement.

Español

Medidas de precaución y advertencias

Producto sanitario para diagnóstico in vitro.
Observe las medidas de precaución habituales para la manipulación de reactivos.
Elimine los residuos según las normas locales vigentes.
Ficha de datos de seguridad a la disposición del usuario profesional que la solicite.

Para los EE.UU.: uso exclusivamente bajo prescripción.

El presente estuche contiene componentes que han sido clasificados por la directiva CE No. 1272/2008 de la siguiente manera:

clorhidrato de 2-metil-2H-isotiazol-3-ona

EUH 208 Puede provocar una reacción alérgica.

Las indicaciones de seguridad del producto corresponden principalmente a las directivas del sistema globalmente armonizado de clasificación y etiquetado de productos químicos (GHS por sus siglas en inglés) válidas en la UE.

ANNEXURE V:SERUM C-REACTIVE PROTEIN KIT

LITERATURE

CRPLX

cobas®

C-Reactive Protein (Latex)

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
20764930 322	C-Reactive Protein (Latex) 300 tests	System-ID 07 6493 0	Roche/Hitachi **cobas c** 311, **cobas c** 501
11355279 216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
10557897 122	Precinorm Protein (3 x 1 mL)	Code 302	
11333127 122	Precipath Protein (3 x 1 mL)	Code 303	
05117003 190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626 190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216 190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774 190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
04489357 190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	

English

System information

CRPLX: ACN 019

Intended use

In vitro test for the quantitative determination of C-reactive protein in human serum and plasma on Roche/Hitachi **cobas c** systems.

Summary[1,2]

Most tissue-damaging processes such as infections, inflammatory diseases and malignant neoplasms are associated with a major acute phase response of the C-reactive protein (CRP) and other acute phase reactants (e.g. AAT, AAGP, C3C, C4, HAPT). The CRP response frequently precedes clinical symptoms, including fever. In normal healthy individuals CRP is a trace protein with a range up to 5 mg/L. After onset of an acute phase response the serum CRP concentration rises rapidly and extensively. Alterations are detectable within 6 to 8 hours and the peak value is reached within 24 to 48 hours. Levels of up to thousandfold the normal value are associated with severe stimuli such as myocardial infarction, major trauma, surgery, or malignant neoplasms.

CRP activates the classical complement pathway. CRP has a half-life of only a few hours, making it an ideal tool for clinical monitoring. Postoperative monitoring of CRP levels of patients indicates either the normal recovery process (decreasing levels to normal) or unexpected complications (persisting high levels). Measuring changes in the concentration of CRP provides useful diagnostic information about how acute and how serious a disease is. It also allows the assessment of complications during the disease and judgements about the disease genesis. Persistence of a high serum CRP concentration is usually a grave prognostic sign which generally indicates the presence of an uncontrolled infection. CRP determination may replace the classical determination of Erythrocytes Sedimentation Rate (ESR), due to its prompt response to changes in disease activity and its good correlation to ESR.

Test principle[3,4,5]

Particle enhanced immunoturbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative

R2 Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative

R1 is in position B, and R2 is in position C.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Mix **cobas c** pack well before placing on the analyzer.

Storage and stability

CRPLX

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks

NaCl Diluent 9 %

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Stability:[6]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at (-15)-(-25) °C

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 311 test definition

Assay type	Rate A
Reaction time / Assay points	10 / 7-18
Wavelength (sub/main)	-/546 nm

CRPLX

C-Reactive Protein (Latex)

cobas®

Reaction direction	Increase		
Units	mg/L (nmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	82 µL	72 µL	
R2	28 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	4 µL	15 µL	75 µL
Increased	2 µL	–	–

cobas c 501 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10 / 12-28		
Wavelength (sub/main)	–/546 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	82 µL	72 µL	
R2	28 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	4 µL	15 µL	75 µL
Increased	2 µL	–	–

Calibration

Calibrators	S1: H_2O S2-S6: C.f.a.s. Proteins
	Multiply the lot-specific C.f.a.s. Proteins calibrator values by the factors below to determine the standard concentrations for the 6-point calibration curve:
	S2: 0.0500 S5: 1.90
	S3: 0.303 S6: 2.50
	S4: 0.907
Calibration mode	Line-graph
Calibration frequency	Full calibration • after reagent lot change • as required following quality control procedures

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).[7]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

Conversion factors:	mg/L x 9.52 = nmol/L	mg/dL x 95.2 = nmol/L
	mg/L x 0.1 = mg/dL	mg/dL x 10 = mg/L
	mg/dL x 0.01 = g/L	g/L x 100 = mg/dL

Limitations - Interference

Criterion: Recovery within ± 10 % of initial values at a CRP concentration of 5.0 mg/L (47.6 nmol/L, 0.5 mg/dL).

Icterus:[8] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[8] No significant interference up to an H index of 500 (approximate hemoglobin concentration: 311 µmol/L or 500 mg/dL).

Lipemia (Intralipid):[8] No significant interference up to an L index of 400. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors up to 1200 IU/mL do not interfere.

High dose hook-effect: No false result occurs up to a CRP concentration of 1000 mg/L (9520 nmol/L, 100 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[9,10]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[11]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on Roche/Hitachi **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/Multiclean/SCCS or the NaOHD/SMS/SmpCln1+2/SCCS Method Sheets. For further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

1.00-250 mg/L (9.52-2380 nmol/L, 0.1-25 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 3.

Lower limits of measurement

Lower detection limit of the test

1.00 mg/L (9.52 nmol/L, 0.1 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying three standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Expected values

Adults[12]	< 5 mg/L	(< 0.5 mg/dL)

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

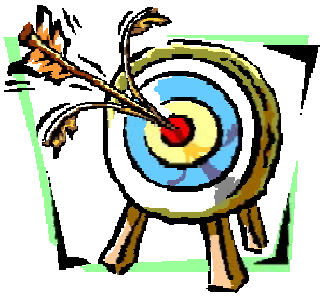
ANNEXTURE VI : MASTER CHART

SL.NO	IP NO	INBORN/OUTBORN	SEX	DAY OF LIFE ON ADMISSION(HOURS)	ADMISSION WEIGHT(gms)	DIAGNOSIS	MODE OF DELIVERY	MATERNAL DATA(PRIMIGRAVIDA/MULTIGRAVIDA)	OBSTRETRIC HISTORY(POG-PERIOD OF GESTATION)	HAEMOGLOBIN (gms/dl)	TOTAL WBC COUNTS (cells/mm^3)	TOTAL PLATELET COUNTS(cells/mm^3)	1^{ST} crp(mg/ltr)	2^{nd} crp(mg/ltr)	PCT(ng/ml)	BLOOD CULTURE
1	838505	INBORN	MALE	00 HRS	1280	PREMATURITY WITH VERY LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	31 WEEKS POG WITH CEPHALIC PRESENTATION WITH ANTEPARTUM HAEMMORHAGE	13	11,600	80,000	74.2	89.3	4.7	*Candida glabrata*
2	839230	INBORN	MALE	00 HRS	1360	PREMATURITY WITH HYPERBILIRUBINEMIA	LSCS	MULTIGRAVIDA	33 WEEKS POG WITH SEVERE PRE-ECLAMPSIA ,IUGR,OLIGOHYDROMNIAS,BREECH PRESENTATION	17.4	9,400	90,000	00.0	0.5	0.2	*No organisms grown in culture*
3	839805	INBORN	FEMALE	OO HRS	1280	PREMATURITY WITH VERY LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	36 WEEKS POG WITH TWIN PREGNANCY WITH CERVICAL STITCH INSITU	17.1	8,500	2,60,000	0.2	1.0	0.6	*Candida glabrata*
4	839806	INBORN	FEMALE	OO HRS	900	PREMATURITY WITH VERY LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	29 WEEKS POG WITH TWIN PREGNANCY WITH PROM WITH CERVICAL STITCH INSITU WITH IVF CONCEPTION	18.2	3,800	1,22,000	0.2	1.2	2.44	*Candida glabrata*
5	840591	OUTBORN	MALE	02 HRS	1800	PRETERM WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	36 WEEKS POG WITH PREVIOUS LSCS	15.9	2,900	10,000	0.1	56.3	2.9	*No organisms grown in culture*
6	840630	OUTBORN	Male	06 hrs	1900	PRETERM WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	36 WEEKS POG WITH PROM	17.8	5,200	2,41,000	0.7	0.6	1.28	*No orgnisms grown in culture*
7	840909	OUTBORN	Male	03 hrs	1500	PRETERM WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	33 WEEKS POG WITH PRE-ECLAMPSIA	15.9	16,500	2,30,000	0.4	236.7	0.31	*No organisms grown in culture*
8	840639		Male	00 hrs	980	PREMATURE WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	33 WEEKS POG WITH CEPHALIN PRESENTATION WITH OLIGOHYDROMNIOS	13.5	9,600	3,30,000	0.2	1.9	10.27	*Candida glabrata*
9	841042	OUTBORN	Female	03 hrs	1500	PREMATURE WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	34 WEEKS POG WITH PROM WITH TWIN GESTATION	20.1	11,700	2,90,000	0.8	0.6	0.5	*No organisms grown in culture*

10	841044	OUTBORN	Male	03 hrs	1500	PREMATURE WITTH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	34 WEEKS POG WITH TWIN GESTATION	15	15,000	3,22,000	0.2	0.9	0.19	*Candida glabrata*
11	840719	Inborn	Male	00 hrs	1600	PREMATURE WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	32 WEEKS POG WITH IUGR WITH OLIGO HYDROMNIOS,PRE-ECLAMPSIA	13.9	5,500	50,000	27.8	6.4	3.8	*Candida glabrata*
12	843246	Inborn	Male	01 hrs	1220	PREMATURE WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	30 WEEKS POG WITH IUGR	19.2	11,000	1,78,000	0.1	2.3	0.32	*No organisms grown in culture*
13	843246	Inborn	Female	01 hrs	1090	PREMATURITY WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	28 WEEKS POG WITH IUGR	18.5	7,100	2,25,000	0.1	56.7	0.23	*Candida tropicalis*
14	844672	Inborn	Female	01 hrs	748	PREMATURITY WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	28 WEEKS POG WITH PV LEAK	15.2	9,300	2,42,000	0.4	27.2	0.59	*Candida tropicalis*
15	843437	Inborn	Female	01 hrs	1330	PREMATURE WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	31 WEEKS POG WITH TWIN PREGNANCY ,IVF CONCEPTION,IUGR	17.2	12,200	3,50,000	0.2	0.1	0.32	*Candida glabrata*
16	845845	Inborn	Female	01 hrs	2650	PREMATURITY WITH HYPERBILIRUBINEMIA	LSCS	MULTIGRAVIDA	32 WEEKS POG BREECH PRESENTATION WITH POLYHYDROMNIOS	15.2	18,300	2,41,000	0.1	3.0	9.07	*No organisms grown in culture*
17	847097	Inborn	Male	00 hrs	1800	PRETERM,LOW BIRTH WEIGHT WITH HYPERBILIRUBINEMIA	LSCS	PRIMIGRAVIDA	30 WEEKS POG WITH SEVER PRE-ECLAMPSIA	12.8	18,000	1,53,000	8.6	184.5	14.64	*Candida tropicalis*
18	846978	Inborn	Male	00hrs	1270	PREMATURITY WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	30 WEEKS POG WITH PROM	17.7	9,000	2,92,000	15.1	68.1	0.27	*Enterobacter species*
19	848414	Inborn	Male	00 hrs	1400	PREMATURITY WITH LOW BIRTH WEIGHT	NORMAL VAGINAL	MULTIGRAVIDA	30 WEEKS POG WITH PROM	19.9	20,700	1,81,000	0.2	13.7	0.2	*Candida tropicalis*
20	846902	Inborn	Male	00 hrs	1350	PRE MATURITY WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	30 WEEKS POG WITH CERVICLE ENCIRCLAGE,PROM	15.2	12,200	2,29,000	61.3	7.3	8.46	*Candida kruzei*
21	848414	Inborn	Male	00 hrs	1400	PREMATURITY WITH LOW BIRTH WEIGHT	NORMAL VAGINAL	PRIMIGRAVIDA	30 WEEKS POG WITH PROM	19.9	21,700	1,80,000	13.7	107.0	0.2	*Candida tropicalis*
22	848736	Inborn	Female	01 hrs	1320	PRMATURITY WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	33 WEEKS POG ,IVF CONCEPTION,TWIN GESTATION,SEVER PRE-ECLAMPSIA,TWIN-1-IUD	12.5	17,900	1,72,000	24.3	16.5	2.29	*Candida tropicalis*
23	850351	Inborn	Male	01 hrs	930	PRETERM WITH LOW BIRTH WEIGHT	NORMAL VAGINAL	PRIMIGRAVIDA	28 WEEKS POG WITH CEPHALIC PRESENATION	17.7	5,300	1,40,000	24.3	22.4	7.40	*Escherichia coli*
24	849835	Inborn	Male	00 hrs	1360	PRETERM WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	30 WEEKS POG .SEVERE PRE-ECLAMPSIA	17.9	10,900	2,89,000	15.0	25.6	1.40	*Candida tropicalis*
25	855545	Inborn	Male	01 hrs	1760	PRETERM WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	36 WEEKS POG ,IUGR,OLIGOHYDROMNIOS,PREVIOUS LSCS	18.6	8,300	2,80,000	0.3	0.2	0.17	*No organisms grown in culture*
26	855898	Inborn	Male	01 hrs	2400	PRETERM WITH INTRA-UTERINE GROWTH RETADATION	LSCS	MULTIGRAVIDA	35 WEEKS POG WITH IUGR	12	15,400	2,49,000	0.2	0.1	0.17	*No organisms grown in culture*
27	884989	Inborn	Female	12 hrs	2100	PRETERM,LOW BIRTH WEIGHT WITH HYPERBILIRUBINEMIA.	LSCS	PRIMIGRAVIDA	34 WEEKS POG WITH SEVERE PRE-ECLAMPSIA	16.8	5,400	28,000	76.1	14.6	2.11	*No organisms grown in culture*
28	885631	Inborn	Female	00 hrs	900	PRETERM WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	32 WEEKS POG BREECH PRESENTATION	15	12,500	2,19,000	22.4	20.4	7.83	*Pseudomonas aeruginosa*

29	885667	Inborn	Female	02 hrs	1900	LATE PRETERM WITH LOW BIRTH WEIGHT	NORMAL VAGINAL	PRIMIGRAVIDA	36 WEEKS POG WITH PRE-ECLAMPSIA	20.3	24,000	1,38,000	0.2	117.0	4.82	*No organisms grown in culture*
30	886459	Inborn	Male	04 hrs	1740	PRETERM,LOW BIRTH WEIGHT WITH HYPERBILIRUBINEMIA	NORMAL VAGINAL	PRIMIGRAVIDA	33 WEEKS POG ,BREECH PRESENTATION	19.7	16,100	2,60,000	0.1	0.0	0.21	*No organisms grown in culture*
31	886323	Outborn	Female	00 hrs	1800	LATE PRETERM WITH LOW BIRTH WEIGHT WITH HYPERBILIRUBINEMIA	LSCS	MULTIGRAVIDA	34 WEEKS POG ,BREECH PRESENTATION,OLIGOHYDROMNIOS	16.9	11,700	4,06,000	0.2	0.1	7.69	*No organisms grown in culture*
32	887108	Inborn	Male	00 hrs	3700	LATE PRETERM WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	37 WEEKS POG WITH CEPHALIC PRESENTATION	15.5	9500	1,04,000	3.8	89.9	12.2	*Staphylococcus epidermidis*
33	886764	Inborn	Female	00 hrs	926	TERM WITH HYPOGLYCEMIA	LSCS	PRIMIGRAVIDA	30 WEEKS POG WITH SEVERE PRE-ECLAMPSIA	15.4	2000	9000	8.0	58.5	5.6	*Klebsiella pneumoniae*
34	886244	Inborn	Male	01 hrs	950	PRETERM WITH LOW BIRTH WEIGHT	LSCS	MULTIGRAVIDA	28 WEEKS POG	14.2	10,800	11,000	50.7	18.6	10.8	*Klebsiella pneumoniae*
35	895366	Inborn	Male	01 hrs	900	PRETERM WITH LOW BIRTH WEIGHT	LSCS	PRIMIGRAVIDA	28 WEEEKS WITH SEVER PIH	15.6	9,400	28,000	1.0	0.6	6.40	*Candida glabrata*
36	895313	inborn	male	02 hrs	2700	TERM WITH HYPOOGLYCEMIA	NORMAL VAGINAL	PRIMIGRAVIDA	39 WEEKS WITH PROM	15.4	12,400	26,000	0.2	1.9	14.62	*Staphylococcus haemolyticus*

Introduction



Objectives

Review of Literature

Methodology

Results

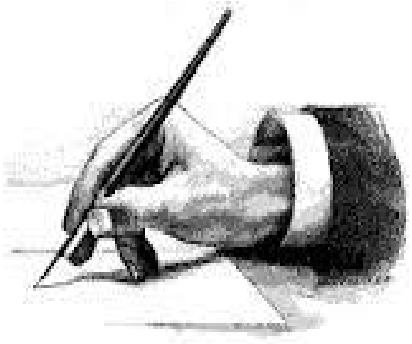
Discussion

Conclusion

Summary

Appendix

Bibliography



Annexures