

Causative Microorganism for Sepsis in NICU

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Research Article

Abstract: Introduction: As many as 2% of foetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life. Infections are a frequent and important cause of neonatal and infant morbidity and mortality. nosocomial infection rates are increasing with an incidence inversely proportional to the gestational ages of the infants populating the NICUs. Causative organisms, Group B *Streptococci* or *Escherichia coli* that are most likely acquired perinatally. The reported incidence of nosocomial sepsis in India ranges from 1.5-37%. Klebsiella emerging as an important cause of nosocomial sepsis. Outcome depends upon weight and maturity of neonate, type of etiologic agent, antibiotic sensitivity and adequacy of specific and supportive therapy. **Material and Methods:** All babies admitted in NICU showing clinical features of sepsis, in whom laboratory investigation support the diagnosis of sepsis. **Study Period:** January 2008 to October 2010. **Study design:** Observational study. **Methods:** Babies enrolled in the study were subjected to laboratory investigations Blood culture and Sensitivity was sent in all babies admitted and if sepsis was suspected. **Conclusion:** Total 1580 neonates were admitted during the study period. Out of these 223 were enrolled in study, Seven neonates were lost during follow up. Fifty neonates of neonatal infection died during the study period. Septic screen was positive in 91.92%, CRP (84.75%), blood culture (74.88%), meningitis(18.8%). Most common organism isolated was Klebsiella pneumoniae (28.7%) and least was streptococcus species (5.3%). Mortality due to neonatal sepsis was 24.4%.

Key Words: Sepsis, Micro-organism, NICU, Mortality.

Introduction

As many as 2% of foetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life. Infections are a frequent and important cause of neonatal and infant morbidity and mortality. Less mature infants are being cared for in neonatal intensive care units (NICUs), nosocomial infection rates are increasing with an incidence inversely proportional to the gestational ages of the infants populating the NICUs. Considering that the smallest, least- mature infants often require the most invasive procedures, have sensitive and immature skin that does not provide a strong barrier against environmental organisms, and immune systems that are marginally responsive to infection from any portal of entry, high-infection rates seem inevitable; but are they? Because neonatal NIs are known causes of morbidity and mortality in all neonates, but particularly in the smallest,

most immature infants, it is important to determine whether the infection risk is inherent to the infant or can be affected by the environment and treatment received in the NICU.(1) The NNIS determined there are causative organisms, particularly Group B *Streptococci* or *Escherichia coli* that are most likely acquired perinatally but do not always cause disease or present with symptoms within the identified time. Nosocomial infections include bloodstream infections, ventilator-acquired pneumonia, urinary tract infections, meningitis, secondary skin infections, and abscesses after skin breakdown or an invasive procedure, and eye, ear, nose, or throat infections. Causative organisms can be bacterial, viral, or fungal in origin. Technically, even *Candida* diaper dermatitis is a NI as it was acquired during the hospital stay and was not perinatally transmitted. Bloodstream infections, frequently with coagulase negative *Staphylococci* and associated with central venous lines, are reported to be the most common NI with an incidence as high as 78% of the total NIs reported. The next most common site varies among NICUs but is often in either the respiratory or urinary tract.¹ Many neonates with strong clinical indicators of sepsis, including severe apnea, lethargy and hypotension, and laboratory abnormalities such as neutropenia, and elevated CRP levels, have a negative blood culture. For this reason, some published studies of neonates include patients with the loosely defined entities “clinical sepsis” or “probable sepsis,” either as a separate group or together with culture proven sepsis. In these patients, the blood culture may be falsely negative or the patient may be experiencing a systemic inflammatory response due to a viral infection or non-infectious process.² The reported incidence of neonatal sepsis varies from 7.113 to 38.17 per 1000 live births in Asia. Neonatal nosocomial infection are important cause of neonatal mortality and morbidity its reporting in India has been non uniform, this may be due to lack of surveillance work and scanty studies on this aspect .the reported incidence of nosocomial sepsis in India ranges from 1.5-37%. Klebsiella emerging as an important cause of nosocomial sepsis.³ Outcome depends

upon weight and maturity of neonate, type of etiologic agent, antibiotic sensitivity and adequacy of specific and supportive therapy. Reported mortality rates in various studies in India are between 45-58% for neonatal sepsis. VLBW infants (< 1,500 g birth weight) have nosocomial infection rates of 20–25%. Rates increase with decreasing gestational age and birth weight. Rates are inversely related to birth weight and range from 11.4 infections/1,000 device days for infants < 1,000 g to 3.8 infections/1,000 device days for those > 2,500 g. Coagulase-negative Staphylococci are the most frequent neonatal nosocomial pathogens.⁴ The aims of this study is to determine the micro-organisms, Laboratory investigation blood culture and sensitivity associated with NICU sepsis and know the Incidence and mortality of sepsis for better outcome of neonates in NICU.

Aims and Objectives

Primary Objective

The study was conducted to evaluate Various Micro-organisms associated with sepsis in neonates admitted in NICU.

Secondary Objective

- 1) To study incidence and immediate outcome of neonatal sepsis.
- 2) Immediate outcome was measured in terms of
 - a. Mortality.
 - b. Commonest organism causing sepsis
 - c. Incidence of culture positive sepsis and culture negative sepsis.

Material and Methods

Place of study

- The study was carried out in level II NICU department of paediatrics Government medical college Aurangabad.

Study Period

- The study was carried during the period of January 2008 to October 2010

Study design

- Observational study.

Sample Size

- All babies who were admitted in NICU during study period and showing clinical features of sepsis >48 hrs of admission.

Inclusion Criteria

The following study population was included in the present study.

All babies admitted in NICU showing clinical features of sepsis >48 hrs of admission, in whom laboratory investigation support the diagnosis of sepsis.

Exclusion Criteria

- 1) Babies having lethal congenital malformation were excluded from the study.

- 2) Babies with maternal history of chorioamnionitis.
- 3) Seriously ill neonate in whom death within 48 hrs was anticipated.

Methods

- Babies enrolled in the study were subjected to detailed clinical examination and history was taken regarding maternal factors as mentioned in proforma.
- Study sample was subjected to laboratory investigations in babies with suspected sepsis which include hemoglobin, total leukocyte count, differential leukocyte count and band Cell Counts, ESR, C-reactive Protein, Urine Examination, X-Ray chest and CSF study when required were done
- Blood culture was sent in all babies admitted and if sepsis was suspected.

Sample collection for Blood culture

Blood culture

As per the CDC guidelines blood samples were collected under aseptic precautions in a blood culture bottle containing culture media. Cultures were collected only from a fresh peripheral veni-puncture site. Approximately 1ml of blood was directly transferred in sterile culture media .All samples were sent to microbiology department where it was inoculated for subcultures.

Examination of CSF

Under all aseptic precautions lumbar puncture was done with number 24 hypodermic needles and CSF was collected in 3 sterile bottles. One of these was fluoride bottle for CSF sugar, other for CSF proteins and third one for microscopy, gram stain and culture sensitivity. Simultaneously, blood sugar sample was collected to compare with CSF sugar.

Other cultures

Patients with sepsis requiring mechanical ventilation in form of bag and tube, endotracheal tube tip culture was sent , angiocath tip culture were also done .

Statistical Analysis

The data was obtained and arranged according to characters during hospitalisation, risk factors for sepsis, symptoms of sepsis duration of development of sepsis, blood culture, organism and outcome.

All data was analysed by using EPI info software and chi-square test, unpaired t-test was applied for significance.

Discussion

Sepsis has been variously defined as “the presence of pathogenic microorganism or their toxins in tissues or blood” or as “a harmful or damaging host

systemic response to infection when the host response to infection becomes enhanced or deregulated.⁵

Bacteremic infection

“A pathological process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms”.⁵

Early-onset Blood stream infection

Infection that occurs within the first 72 hrs of life usually reflecting vertical transmission.

Late-onset Bloodstream infection

Infection that occurs after 72 hrs of life usually reflecting horizontal transmission.

Nosocomial Blood stream infection

An infection that occurs >48 hrs after admission in a baby who did not have evidence of an infection on admission, characterized by growth of a pathogen not related to infection at another site from one blood culture or a positive PCR in the presence of clinical features of infection.⁵ Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life.⁶

Clinical Features

Sepsis in neonates may be 1) Acquired from mother (transplacental route).²

Table 1: Micro-organism and Manifestations

Manifestation	Pathogen
Intrauterine Growth Restriction	CMV, Plasmodium, rubella, toxoplasmosis, Treponema pallidum, Trypanosoma cruzi, VZV
Congenital Anatomic Defects	
Cataracts	Rubella
Heart defects	Rubella
Hydrocephalus	HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis
Intracranial calcification	CMV, HIV, toxoplasmosis, T. Cruzi
Limb hypoplasia	VZV
Microcephaly	CMV, HSV, rubella, toxoplasmosis
Microphthalmos	CMV, rubella, toxoplasmosis

2) Early onset caused by organisms prevalent in the maternal genital tract or in delivery area, manifests commonly as pneumonia less commonly as septicemia or meningitis.²

3) Late onset sepsis presents as septicemia, pneumonia or meningitis.²

Manifestations of neonatal sepsis are often vague and illdefined hence early diagnosis is necessary. Common and early but nonspecific manifestation is alteration in established feeding behavior.³

The clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely,

congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease. Maternal infection that is the source of transplacental fetal infection is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas. Manifestation included temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. The initial manifestation may involve only limited symptomatology and only 1 system, such as apnea alone or tachypnea with retractions or tachycardia, or it may be an acute catastrophic manifestation with multiorgan dysfunction. Infants should be re-evaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).² Complications of neonatal sepsis can include metastatic focus of infection, disseminated intravascular coagulation and congestive heart failure. Reese Clark *et al* in 2004 The dominant presenting features of septicemia or sepsis include: increasing apnea (55%); feeding intolerance, abdominal distension, or guaiac-positive stools (43%); need for increased respiratory support (29%); and lethargy and hypotonia (23%).⁷ The incidence of neonatal bacterial sepsis is 9.8 per 1000 livebirths. E. coli and Klebsiella were the most common organisms causing EOS and LOS, respectively: E. fecalis was also a major pathogen, both in EOS and LOS.⁸ Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS, enteric organisms, gonococci, and chlamydiae. The more common viruses are CMV, HSV, and HIV. Agents that commonly cause nosocomial infection are coagulase-negative staphylococci, gram-negative bacilli (E. coli, Klebsiella pneumoniae, Salmonella, Enterobacter, Citrobacter, Pseudomonas aeruginosa, Serratia, enterococci, S. aureus, and Candida. Viruses contributing to nosocomial neonatal infection include enteroviruses, CMV, hepatitis A, adenoviruses, influenza, respiratory syncytial virus, rhinovirus, parainfluenza, HSV, and

rotavirus. Community-acquired pathogens such as *Streptococcus pneumoniae* may also cause infection in newborn infants after discharge from the hospital.² Abed El Hakeem Noman El Jadba, Mansour Sobhi El Yazji in 2009 studied prospective descriptive study was carried out in (NICU) in Al-Nasser and Al-Shifa hospitals in Gaza City, between January 2004 to January 2005. Three hundred twenty eight neonates out of 2487 cases had positive blood cultures with infection rate of 13.2%. prevalence of Coagulase negative staphylococci (57.3%), *E. coli* (10.4%), *Klebsiella* spp. (8.0%) and others (24.3%).⁹ Shaw CK *et al* (2007) done retrospective study over a period of six years to study the prevalence of different organisms causing septicaemia. One hundred nineteen cultures out of the 131 positives were obtained from blood (44.92%) and the remaining were isolated from urine (6.11 %) and CSF (4.58 %). The most common organism to be isolated was staphylococcus aureus (42.75%) followed by *klebsiella pneumoniae* (18.32%) and *escherechia coli* (12.21%).¹⁰ Shubhra Singh *et al* noticed that for last 20 years Coagulase negative staphylococci (CoNS) have been identified as major causes of late-onset neonatal bacteraemia in new born intensive care units and studied 1087 cases admitted in the NICU of the Gandhi Memorial and associated hospitals, Lucknow during the period of September 2005 to December 2007. Cases included in study were neonates (of age less than or equal to 28 days) suspected to be suffering from the septicemia on the clinical grounds. Samples taken were blood, pus, nasal aspirate, urine and catheter tip. In their study Co-agulase negative staphylococcus (14.09%) and *S. aureus* (11%) were most common gram positive isolates and *Klebsiella*.spp (20.8%), *E.coli* (15.57%) and *Pseudomonas* spp (15.70%) were most common gram negative organism Biotyping was done for all the CoNS isolates. In biotyping *S. epidermidis* (40%) was the most common species followed by *S. saprophyticus* (20%) and *S. haemolyticus* (12%).¹¹ Ludo M. Mahieu, *et al* in 2001 did study to identify risk factors and describe the microbiology of catheter exit-site and hub colonization in neonates. The pathogens responsible for catheter exit site and hub colonization. Gram-positive organisms, especially coagulase-negative staphylococci, were the organisms most commonly isolated at the exit site and the hub with a high predominance of *Staphylococcus epidermidis*, followed by *Staphylococcus hominis* and *Staphylococcus aureus*. *Candida albicans* was encountered in only one case. As opposed to the exit-site colonization, the hub was more commonly colonized with pathogenic flora, eg, *S aureus*, *Enterococcus fecalis*, and gram-negative organisms (36% vs 14%; P<.05). It was found that the site of catheter insertion or duration of placement did not

influence the microbiology of exit-site colonization.¹² S vergnano *et al* studied that pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram negative organisms are more common and are mainly represented by *Klebsiella*, *Escherichia coli*, *Pseudomonas*, and *Salmonella*. Of the Gram positive organisms, *Staphylococcus aureus*, coagulase negative staphylococci (CONS), *Streptococcus pneumoniae*, and *Streptococcus pyogenes* are most commonly isolate.¹³ Payman Salamati *et al* in 2006 studied neonatal nosocomial infection in Bahrami Children Hospital and found most common pathogenic organisms were *Enterobacter* (27%), *aures Staphylococcus* (21%), *Klebsiella* (18%), *E.coli* (14%) and *epidermis Staphylococcus* (9%).¹⁴ Duha Sabeeh Jumah and Me'ad Kadhum Hassan studied *Klebsiella* was the commonest bacteria isolated in 38(36.6%), followed by *E. coli* 33(27.5%), and *E.aeruginosa* 27(22.5%). Other bacteria were *Proteus* in 13(10.8%), group B streptococci, *Staphylococcus aureus* and *Pseudomonas aeruginosa* in 3 neonates for each (2.5%).¹⁵ Kapoor L *et al* in Sep 2005 studied over a period of one year (July 2000 to June 2001), Gram-negative bacteria were the predominant isolates (62%), commonest being *Klebsiella pneumoniae* (34%) followed by *E. coli* (17%), *Acinetobacter* spp. (9%) and *Enterobacter aerogenes* (2%). Gram-positive cocci were isolated in 20% cases, of which coagulase negative staphylococcus was the predominant isolate (11%) followed by *Enterococcus* spp. (5%) and *S. aureus* (4%). *Candida* spp. was isolated from 18% of cases.¹⁶

Organisms Isolated In Sepsis: (refer in table no 2 Review)

In present study 74% neonates had culture positive sepsis. Among these *Klebsiella pneumoniae* (28.7) was most common organism isolated. *E.coil* was second most common organism (22.1%).*Streptococcus species* (5.3%) was least common organism isolated. In a study¹⁶ 76% neonates had culture positive sepsis. *Klebsiella* was the commonest organism isolated (68%) followed by *Pseudomonas* (13%). In another study¹⁷ *Klebsiella pneumoniae* was isolated in 47.7% neonates, followed by *Staphylococcus aureus* in 40.09%,*Streptococcus* species in 2.4% neonates. In a study⁸ *Klebsiella* was isolated in 36.6% neonates, followed by *E.coli* in 27.5% neonates. In another study⁴⁴ most common organism isolated in nosocomial sepsis was *Staphalococcus aureus* (42.75%) followed by *Klebsiella* (18.32%) and *E.coli* (12.21%). In a study⁴⁸ most common organism isolated was *Enterobacter* (27%), followed by *staphalococcus* (21%), *klebsiella* (18%), *E.coli* (14%) and the least was CONS (9%). In another study⁶ CONS 30% were most common organism isolated, followed by *Klebsiella pneumoniae*

(20%). In a study⁵², E.coli was most common organism isolated. It is due to fact that it is common commensal of intestine and vaginal flora, Differences in observations are due to most deliveries conducted at home presumably under condition of poor hygiene. In another study¹⁷, 19%

of neonates were given antibiotic before collection of sample. Over dilution of little blood in broth bottles may also hinders some growth.

There are significant differences in methodology used when comparing infection rates.

Table 2: Micro-Organism Of Sepsis

	Abd Hakeem	Shaw Ck	Shubhra Singh	Payman Salamain	Duha Sabech	Irregu	Laparo
CONS.	57.3%	-	14.09%	9%	-	-	-
Staphylococc	5	42.75%	11%	21%	-	81%	4%
E-coli	10.4%	12.2%	15.5%	1.4%	33 (27.5%)	-	17%
Klebsilla Spect	8%	18.32%	20.8	18%	38 (36.6%)	86%	34%
Others	24.3%	-	-	-	13 (10.8%)	-	-
Pseudomonas	-	-	15.7%	-	2.5%	-	-
Enterobacter	-	-	-	27%	-	-	-
Candida	-	-	-	-	-	-	18%

Investigations

It is important that the supportive and antimicrobial therapy of a neonate with sepsis is instituted quickly. Hence minimum and rapid investigations should be undertaken. Blood culture: It is the gold standard for the diagnosis of septicemia and should be done in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture and sensitivity of the isolate is the best guide to antimicrobial therapy.

Table 3: A practical sepsis screen Components Abnormal value

Total leukocyte count <5000/mm3
Absolute neutrophil count
Immature/total neutrophil >0.2
Micro-ESR > 15 mm in 1st hour
C reactive protein (CRP) >10 mg/dl

Since clinical features of sepsis and meningitis are non-specific in neonates, it is likely that meningitis

may be present without specific symptomatology along with sepsis

Results

All neonates admitted in NICU during the study period were screened. Total 1580 neonates were admitted during the study period. Out of these, 223 met the inclusion criteria, 7 neonates were lost during follow up and 50 neonates died. 250 neonates were selected as control group matched with cases for weight and gestational age and not having any clinical or laboratory evidence of sepsis.

➤ In present study incidence of sepsis was 14.11% (223/1580), Most common organism isolated was Klebsiella pneumoniae (28.7%) and least was streptococcus species (5.3%).with the mortality of 22.4% (50/223).

Table 4: Sex Distribution in Sepsis

Sex	With Sepsis(n=223)		Without sepsis(n=250)		P value	Relative Risk	Odds Ratio
	Frequency	Percentage	Frequency	Percentage			
F	88	39.5	139	55.6	<0.05	0.71	0.52
M	135	60.5	111	44.4			

There was preponderance of sepsis in males neonates, M:F=1.5:1

Table 5: Weight Distribution with Sepsis

Weight Distribution	With Sepsis (n=223)		Without sepsis (n=250)	
	Frequency	Percentage	Frequency	Percentage
ELBW	9	4	7	2.8
VLBW	114	51.1	63	26.2
LBW	68	30.5	121	48.4
Normal	32	14.3	59	23.6

VLBW neonates were most commonly affected.

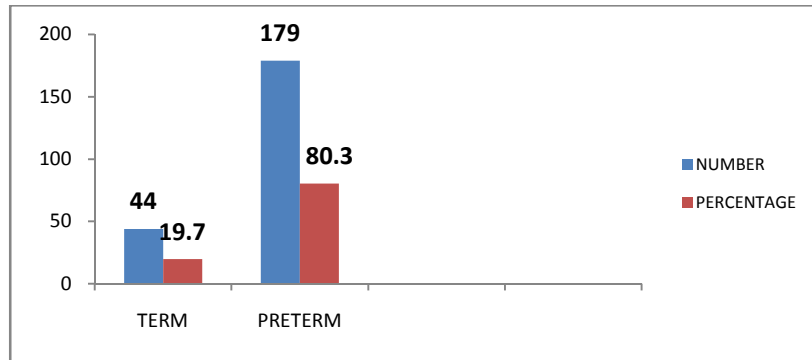


Figure 1: Prematurity with Sepsis

Neonatal sepsis is common in preterms.

Table 6: Gestation Age with Sepsis

Gestational Age(weeks)	With Nosocomial sepsis (n=223)		Without Nosocomial sepsis (n=250)	
	Frequency	%	Frequency	%
28-30	21	9.4	16	6.4
30-32	22	9.9	16	6.4
32-34	59	26.5	47	18.8
34-36	61	27.3	54	21.6
>37-42	44	19.7	94	37.6
>42	16	7.1	23	9.2

Neonatal sepsis was most common in 34-36 week gestational age neonates.

Table 7: Cultures Associated with Neonatal Sepsis

Sr. No.	Cultures	With Sepsis (n=223)		Without sepsis (n=250)	
		Frequency	Percentage	Frequency	Percentage
1	Blood Culture				
	Positive	56	25.12%	0	0
	Negative	167	74.88%	250	100
2	CSF Culture (n=167)				
	Positive	15	8.98	232	92.8
	Negative	152	91.01	18	7.2
3	IVC Culture (n=80)				
	Negative	69	86.25%	75	93.75
	Positive	11	13.75%	5	6.66
4	Endotracheal Tip Culture (n=65)				
	Positive	13	20%	3	4.61
	Negative	52	80%	62	95.38

Blood culture was positive in 167 (74.88%), CSF culture 15 (8.9%), IVC culture 11 (13.75%) ET tube culture 13 neonates (20%).

Table 8: Neonatal Sepsis and Outcome

Outcome	With Sepsis (n=223)		Without sepsis (n=250)	
	Frequency	Percentage	Frequency	Percentage
AMA	7	3.2	-	-
Cured	166	74.4	203	81.2
Expired	50	22.4	47	18.8
Total	223	100%	250	100%

In the present study mortality due to Neonatal infection was 22.4%.

Summary and Conclusions

- Total 1580 neonates were admitted during the study period. Out of these 223 met the inclusion and exclusion criteria and either of their parents gave consent to participate in the study.
- Seven neonates were lost during follow up.
- Fifty neonates of neonatal infection died during the study period.
- Septic screen was positive in 91.92%, CRP (84.75%), blood culture(74.88%), meningitis(18.8%).
- Most common organism isolated was *Klebsiella pneumoniae* (28.7%) and least was streptococcus species (5.3%).
- Mortality due to neonatal sepsis was 24.4%.

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