Original Research Article

Study of blood culture isolates from neonatal septicaemia

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Abstract

Introduction: Neonatal septicemia is classified as early onset sepsis (EOS) and late onset sepsis (LOS). The signs and symptoms of neonatal sepsis are non-specific but sepsis may rapidly progress and worsen, and may cause death within a few hours to days. Blood culture, which is the gold standard for definitive diagnosis, takes at least 48 hours up to 6 days, by which time the infection may have progressed with consequences on the morbidity and mortality of the neonates. **Material & Methods:** The present study was conducted in the Department of Microbiology, Tertiary care teaching hospital after approval from institutional ethics committee. Blood sample was collected from the patients admitted in Neonatal Intensive Care Unit (NICU) of same hospital. All clinically suspected patients of neonatal septicemia admitted in NICU of our hospital. **Results:** Out of the total 412 blood samples received 238 (57.77%) were males and (42.23%) were females. Male to female ratio is 1.36:1. Major risk factor associated with in early-onset neonatal septicemia were found to be birth weight less than 2.5Kg 134 (53.60%), preterm birth 116 (46.40%), increased duration of labour 112 (44.80%) and Birth asphyxia 106 (42.40%). Out of 412 clinically suspected neonatal septicemia patients 138 (33.49%) were found culture positive. Out of 138 culture positive samples the Gram negative bacteria were 94 (68.12%) and Gram positive bacteria were 44 (31.88%) found. **Conclusion:** Early onset neonatal septicemia (EOS) was more common than late onset neonatal septicemia (LOS). Overall Gram negative isolates were the predominant causative agents for neonatal septicemia. *Klebsiella pneumoniae* was the most common Gram negative isolate and *Staphylococcus aureus* was most common Gram positive isolate.

Keywords: Neonatal septicaemia, Blood culture, Antimicrobial susceptibility testing.

Introduction

Neonatal death is not only sensitive issue in connection with society but also a challenge to health care system. Neonatal mortality rate is one of the indicator for measuring the health status of a nation. [1] In 2015 worldwide neonatal mortality rate was 19 deaths per 1,000 live births and an estimated 2.7 million deaths occurred in the neonatal period globally. [2] Among all neonatal deaths globally, one-quarter are attributed to infectious cause. [3] Infections in the newborn period typically include pneumonia, sepsis, and those of the umbilical cor. Neonatal sepsis attribute 15% of total neonatal deaths globally. [4] India contributes to around one-quarter of all neonatal deaths in the World and more than half (52%) of these are estimated to occur due to infections. [5] In 2014 neonatal mortality rate in India was 26 deaths per 1000 live births. [6]

In 2012, 15%deaths of neonates were due to sepsis. [7] In Maharashtra in 2014 neonatal mortality rate was 16 deaths per 1000 live births. [8]

Neonatal septicemia is classified as early onset sepsis (EOS) and late onset sepsis (LOS). The signs and symptoms of neonatal sepsis are non-specific but sepsis may rapidly progress and worsen, and may cause death within a few hours to days. [9] This is why, adequate and timely diagnosis of neonatal sepsis remains an important challenge to the clinician especially in developing countries. [10] Blood culture, which is the gold standard for definitive diagnosis, takes at least 48 hours up to 6 days, by which time the infection may have progressed with consequences on the morbidity and mortality of the neonates. [11]

Various inflammatory markers and haematological indices have also been used in diagnosing neonatal sepsis. Inflammatory indices such as C–reactive proteins (CRP), procalcitonin, presepsin serum CXCR4 and CXCL12, 25-OH vitamin D studied worldwide. [12] Haematological scoring system (HSS) based on Fructose-1, 6-bisphosphatase (FBP), total leukocyte count, neutrophils and platelets have also been used to predict neonatal sepsis. [13] A number of biomarkers have been studied for the diagnosis of sepsis in pediatrics, but no gold standard has been identified. [14] Also none had achieved rapid and reliable enough identification specialty of infected neonates. [15]

Early diagnosis, isolation of microbes from blood and their antimicrobial susceptibility test is very essential to reduce rate of neonatal mortality due to septicemia. [16] Blood culture is the gold standard for diagnosis and should be performed in all patients of suspected septicemia prior to starting antibiotics. [17] But septicemia in a neonate is a medical emergency and generally the clinicians do not wait for microbiology report and start treatment empirically. [18] Also susceptibility pattern of the organisms varies with the geographical area. [19] It is also different in each hospital and region. Microorganisms implicated in neonatal septicemia have developed increased drug resistance to commonly used antibiotics and thus making treatment extremely difficulty. [20]

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Material & methods

The present study was conducted in the Department of Microbiology, Tertiary care teaching hospital after approval from institutional ethics committee. Blood sample was collected from the patients admitted in Neonatal Intensive Care Unit (NICU) of same hospital.

Inclusion Criteria

All clinically suspected patients of neonatal septicemia admitted in NICU of our hospital.

Exclusion Criteria

1. Parents of neonate not willing to participate in this study.
2. Patients who underwent surgery.
3. Neonates with lethal congenital anomalies.

Blood Sample Collection:

About 3 ml of blood was withdrawn using sterile syringe. Two ml of blood was inoculated aseptically into blood culture bottles containing 10 ml Brain Heart Infusion broth (BHI) achieving dilution of 1 in 5 to nullify the natural bacteriostatic/bacteriocidal activity of blood. Remaining 1 ml of blood was allowed to clot in sterile bottle for separation of serum. This serum was used to test CRP.

Processing of Samples

The inoculated blood culture bottles were incubated at 37ºC under aerobic condition for 7 days. The first subculture was done after 24 hours of incubation, the second subculture done on third day and final subculture was done on seventh day.

Culture

Subcultures were done on Nutrient agar, Blood agar, and MacConkey agar.

Incubation

The inoculated plates were incubated aerobically in the incubator at 35-37ºC for 18- 24 hours, and the plates were observed for growth. A provisional report was issued after first subculture and if no growth is observed after 7 days, the sample reported as negative. If growth was observed on inoculated plates, the organisms were identified on the basis of colony characteristics, Gram's staining and biochemical test as per standard bacteriological techniques. Quality control of all used media where done by standard protocol.

Antimicrobial Susceptibility Test

Antimicrobial susceptibility testing of all identified isolates was done as per "Performance Standards for Antimicrobial Susceptibility Testing CLSI document M100-S25.CLSI 2015 guidelines" using Kirby- Bauer disk diffusion method on Mueller Hinton agar. Isolates were grown in peptone water by incubating at 37º C and turbidity was matched with 0.5 MacFarland standards. Using sterile swab stick lawn culture was done on Mueller Hinton agar plate. Commercially available antimicrobial disks were placed. After 18-24 hours of incubation at 37º C zone size was measured. Isolate is susceptible or resistant was decided according 2015 CLSI guidelines.

Results

This study was conducted in Department of Microbiology of tertiary care hospital. A Total of 412 blood samples from clinically suspected neonates from NICU were processed. The result of the study is illustrated as follows.

Table 1: Distribution According to Age and Sex in Clinically Suspected Neonatal Septicemia Patients (n=412)

Age group (days)	Male (%)	Female (%)	Total (%)
1- 3	154(64.70)	104(59.77)	258(62.62)
4 - 7	14(5.88)	8(4.59)	22(5.34)
8 - 14	53(22.27)	42(24.14)	95(23.06)
15 - 28	17(7.14)	20(11.49)	37(8.98)
Total	**238 (57.77)**	**174 (42.23)**	**412 (100)**

Out of the total 412 blood samples received 238 (57.77%) were males and (42.23%) were females. Male to female ratio is 1.36:1

Table 2: Distribution of Risk Factors in Early-Onset Neonatal Septicemia (N=258)

Risk factor	Culture Positive n=88 (%)	Culture Negative n=170 (%)	Total n=258(%)
Maternal fever	18 (20.56)	12 (07.06)	30 (12.00)
Unclean vaginal examination	32 (36.36)	42 (24.71)	74 (27.60)
Premature rupture of membrane	38 (43.18)	32 (18.82)	70 (28.00)
Foul smelling liquor	32 (36.36)	30 (17.65)	62 (24.80)
Duration of labour (>24hours)	38 (43.18)	74 (43.53)	112 (44.80)
Birth asphyxia (Apgar score at 1min)	38 (43.18)	68 (40.00)	106 (42.40)
Preterm (<37 weeks)	44 (50.00)	72 (42.35)	116 (46.40)
Birth weight (<2.5Kg)	52 (59.09)	82 (48.24)	134 (53.60)

Major risk factor associated with in early-onset neonatal septicemia were found to be birth weight less than 2.5Kg 134 (53.60%), preterm birth 116 (46.40%), increased duration of labour 112 (44.80%) and Birth asphyxia 106 (42.40%).

Table 3: Distribution of Risk Factors in Late-Onset Neonatal Septicemia (n=154)

Risk factor	Culture Positive n=50 (%)	Culture Negative n=104 (%)	Total n=154(%)
Preterm (<37 weeks)	38 (76.00)	74 (71.15)	112 (72.73)
Birth weight (<2.5Kg)	39 (78.00)	88 (84.62)	127 (82.47)
Top feeding	6 (12.00)	61 (58.65)	67 (43.51)
Other site infection (GIT, Respiratory tract, skin, IV site infection)	24 (48.00)	23 (22.12)	47 (30.52)

Major risk factor associated with in late-onset neonatal septicemia were found to be birth weight less than 2.5Kg 127 (82.47%), preterm birth 112 (72.73%).

Table 4: Distribution of Organisms According To Onset of Septicemia in Culture Positive Neonatal Septicemia Patients (n=138)

Organism	Early-onset n=88 (%)	Late-onset n=50 (%)	Total n=138 (%)
Klebsiella pneumonia	29 (32.96)	9 (18.00)	38 (27.54)
Escherichia coli	27 (30.68)	8 (16.00)	35 (25.36)
Staphylococcus aureus	22 (25.00)	6 (12.00)	28 (20.29)
CoNS	02 (2.27)	11 (22.00)	13 (09.42)
Pseudomonas aeruginosa	02 (2.27)	10 (20.00)	12 (08.70)

Citrobacter species	02 (2.27)	02 (04.00)	04 (02.90)
Enterobacter species	01 (1.14)	02 (04.00)	03 (02.17)
Enterococcus species	02 (2.27)	01 (02.00)	03 (02.17)
Acinetobacter species	01 (1.14)	01 (02.00)	02 (01.45)

Out of 412 clinically suspected neonatal septicemia patients 138 (33.49%) were found culture positive. Out of 138 culture positive samples the Gram negative bacteria were 94 (68.12%) and Gram positive bacteria were 44 (31.88%) found.

*Klebsiella pneumonia*is found to be most common isolate38 (27.54%) followed by *Escherichia coli*35 (25.36%) and *Staphylococcus aureus*28 (20.29%).

In early onset neonatal septicemia most common pathogen was found to be *Klebsiella pneumonia*29 (32.96%), *Escherichia coli*27 (30.68%)and *Staphylococcus aureus*22 (25.00%)

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Table 5: Antimicrobial Susceptibility Pattern of Non-Fermenter Isolates In Culture Positive Neonatal Septicemia Patients (n=14)

Antibiotic	*Pseudomonas aeruginosa* n=12 (%)	*Acinetobacterspp* n=02 (%)
Piperacillin (100 µg)	04 (33.33)	01 (50.00)
Ceftazidime (30µg)	06 (50.00)	02 (100)
Cefepime (30µg)	06 (50.00)	02 (100)
Aztreonam (30µg)	10 (83.33)	02 (100)
Imipenem (10µg)	10 (83.33)	02 (100)
Gentamicin (10µg)	03 (25.00)	01 (50.00)
Tobramycin (10µg)	05 (41.66)	01 (50.00)
Amikacin (30µg)	03 (25.00)	01 (50.00)
Ciprofloxacin (5µg)	04 (33.33)	02 (100)
Cefoxitin (30µg)	06 (50.00)	02 (100)

*Pseudomonas aeruginosa*is most sensitive to Imipenem and Aztreonam 10 (83.33%).*Pseudomonas aeruginosa*is most resistant to gentamicin 3 (25%)

Acinetobacter spp is 100% sensitive to Ceftazidime, Cefepime, Aztreonam, Imipenem, Ciprofloxacin and Cefoxitin. While 50% sensitive to Piperacillin, Gentamicin, Tobramycin, Amikacin,

Table 6: ESBL Producer Among The *K. pneumoniae* AND *E. coli* in Neonatal Septicemia Patients

Organism	*K. pneumoniae*	*E. coli*	Total
ESBL Producers	16 (42.10)	13 (37.14)	29 (39.73)
ESBL Non-Producers	22 (57.90)	22 (62.86)	44 (60.27)
Total	**38 (100)**	**35 (100)**	**73 (100)**

Resistance mechanism by ESBL production seen in *Klebsiella pneumonia* is 42.10% and *in Escherichia coli* is 37.14%**.**Total 29 (39.73%) of enterobacteriacae are ESBL producers

Table 7: Distribution of CRP With Age of Onset in Neonatal Septicemia

Age of onset	CRP Positive	CRP Negative	Total
EOS	163 (67.08)	95 (56.21)	258
LOS	80 (32.92)	74 (43.79)	154
Total	**157**	**255**	**412**

CRP test was positive in 163 (67.08%) of early onset septicemia patients while 80 (32.92%) in late onset septicemia patients.

Table 8: Antimicrobial Susceptibilitypattern of Gram Positive Isolates in Culture Positive Neonatal Septicemia Patients (n=44)

Antibiotic discs (concentration)	*Staphylococcus aureus* n=28 (%)	*CoNS* n=13 (%)	*Enterococcus Species* n=03 (%)
Penicillin (10 units)	04 (14.29)	00 (00.00)	00 (00.00)
Ampicillin (10 µg)	04 (14.29)	00 (00.00)	00 (00.00)
Cefoxitin (30 µg)	11 (39.29)	02 (15.38)	--
Vancomycin (30 µg)	28 (100)	13(100)	03(100)
Teicoplanin(30 µg)	28 (100)	13(100)	03(100)
Erythromycin (15 µg)	10(35.71)	3(23.07)	01(33.33)
Clindamycin (2 µg)	17 (60.71)	10(76.92)	03(100)
Gentamicin (10 µg)	17(60.71)	05(38.46)	--
Gentamicin (120 µg)	--	--	02 (66.66)
Amikacin(30 µg)	21(75)	05(38.46)	--
Tetracycline (30 µg)	11 (39.29)	06(46.15)	2(66.66)
Ciprofloxacin(5µg)	12(42.86)	10(76.92)	2(66.66)
Cotrimoxazole (Trimethoprim Sulfamethoxazole) (1.25/23.75 µg)	14(50)	06(46.15)	--
Linezolid (30 µg)	28 (100)	13(100)	03 (100)

Isolates of *Staphylococcus aureus* were 100% sensitive to Linezolid, Vancomycin and Teicoplanin.*Staphylococcus aureus* were most resistance to Penicillin (14.29%) and Ampicillin(14.29%). Routinely used antimicrobials such as Clindamycin ,Amikacin and Gentamicin were moderately effective. Out of 28*Staphylococcus aureus*17 (60.71%) were Methicillin Resistance Staphylococcus aureus (MRSA).

Isolates of *Coagulase negative Staphylococcus* were 100% sensitive toVancomycin, Teicoplanin and Linezolid. WhileCoNS were 100% resistant to Penicillin and Ampicillin

Isolates of *Enterococcus Species* were 100% sensitive to Vancomycin, Teicoplanin, Clindamycin, Linezolid.Isolates of *Enterococcus Species* were 100% resistant to Penicillin, Ampicillin. Out of 3 *Enterococcus Species* 1(33.33%) was High Level Aminoglycoside Resistance (HLAR).

Discussion

In every study male are more commonly affected than female. In our study male to female ratio is 1.36:1 which is near to with studies of Valinjkar et al (1.40:1) and Sharma et al (1.32:1). [21]

In our study, most common risk factor for EOS was Birth weight <2.5Kg (53.60%) which is consistent with Shah GS et al (55.20%). Followed by preterm baby (46.40%), duration of labour >24hours (44.80%) and Birth asphyxia (42.40%) which is consistent with Vinodkumar et al. [22,23] In our study most common risk factor to cause LOS was preterm baby <37 weeks (72.73%) and Birth weight <2.5Kg (82.47%) which is nearly same with Jain et al and Zwaini et al. [24]

In our study most common isolate was *Klebsiella pneumoniae* (27.54%) which is consistent with Sundarapandian et al (27.80%). [25] Also in our studies E. coli (25.36%) and S. aureus (20.29%) is consistent with Upadhyay et al (27.5%) and Ullah et al (19.50%) respectively. [26,27] Maximum studies shows Non-fermenters like *Pseudomonas* and *Acinetobacter* were less isolated. In our study also Non-fermenters like *Pseudomonas* and *Acinetobacter* were isolated less. But Upadhyay et al(193) shows large percentage of *Pseudomonas* were isolated.

Coagulase Negative Staphylococcus is usually considered contamination due to improper cleansing of venipuncture site. As per Hammerberg et al if enough care is taken to avoid contamination CoNS are considered as infective agents. [27] So as in our study we were assured of all aseptic precautions we considered CoNS as causative agent of septicemia. Also, this view is supported by Favre et al who concluded their study reporting that CoNS bacteremia harbor a significant mortality and a single positive blood culture in the presence of signs of sepsis should be considered as clinically relevant. [28]

In our study *Enterobacter* species and *Enterococcus* species were isolated. Majority of studies did not isolated *Enterobacter* species and *Enterococcus* species except for few studies like Sharma Chandra et al who isolated *Enterobacter* species. While Vaniya et al(37) and Mehta et al isolated *Enterococcus* species. [29]

In our study *Staphylococcus aureus* were 100% sensitive to Linezolid, Vancomycin and Teicoplanin. It is consistent with finding of Muley et al which were 100% sensitive to Linezolid and Vancomycin. Unlike other studies Mehta et al reported high rate of sensitivity to Cefoxitin (90%). In our study *Staphylococcus aureus* were most resistance to Penicillin (85.71%) and Ampicillin (85.71%) this is consistent with Mehta et al which reported resistant to Ampicillin of 87.37%. [30] Study Muley et al reported 72.70% of resistance to Penicillin. In our study routinely used antimicrobials such as Clindamycin, Amikacin and Gentamicin were moderately effective against *Staphylococcus aureus*. [31]

In our study isolates of *Coagulase negative Staphylococcus* were 100% sensitive to Vancomycin, Teicoplanin and Linezolid. It is consistent with finding of Muley et al and Roy et al. [32] Also Khan et al showed 100% sensitivity of CoNS to Vancomycin. [33] In our study CoNS were 100% resistant to Penicillin and Ampicillin. This is in accordance with Khan et al which reported 100% resistance of CoNS to Penicillin. Study by Muley et al showed 72.70% of resistance to Penicillin. [34]

In our study isolates of *Enterococcus Species* were 100% sensitive to Vancomycin, Teicoplanin, Clindamycin, Linezolid. It is consistent with finding of Muley et al. [35] In our study isolates of *Enterococcus Species* were 100% resistant to Penicillin, Ampicillin. Maximum studies reported glycopeptide like Teicoplanin and Vancomycin are almost 100% effective against all Gram positive isolates. Mahmood et al reported that Gram positive isolates showed 89.23% sensitivity to Amikacin and 100% sensitivity to Vancomycin. [36]

Conclusion

Early onset neonatal septicemia (EOS) was more common than late onset neonatal septicemia (LOS). Overall Gram negative isolates were the predominant causative agents for neonatal septicemia. *Klebsiella pneumoniae* was the most common Gram negative isolate and *Staphylococcus aureus* was most common Gram positive isolate. In our study resistance mechanism by ESBL production was seen in *Klebsiella pneumonia* was 42.10% and *in Escherichia coli* was 37.14%. While 60.71% were Methicillin Resistance Staphylococcus aureus (MRSA).

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