

Original Articles

Study on Bacteriological Profile and Sensitivity Pattern of the Organisms in Neonatal Sepsis

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Abstract:

Background: Sepsis in neonates by resistant strains remains a significant cause of mortality and morbidity in developing countries. This study attempted to find out the organisms responsible for early onset sepsis (EOS) and late onset sepsis (LOS) and determine their antimicrobial sensitivity pattern.

Materials & Methods: This prospective observational single centre study was conducted on 1000 neonates during January to September 2018, that were investigated for rule out sepsis, at the Neonatal Intensive Care Unit of Ad-din Medical College Hospital, Dhaka.

Results: Fifty-four neonates were found with culture proven sepsis. Coagulase-negative Staphylococci (CONS) (68.42%) was the commonest and followed by Acinetobacter (18.42%) were found on culture isolates in EOS. In LOS, CONS (75%) is the most predominant organism. Among the gram negative Acinetobacter (50%) was the most prevalent bacteria followed by E.coli (28.57%). None of the gram positive isolates were sensitive to Amikacin. Majority of the gram positive showed susceptibilities to Vancomycin (83%) and Linezolid (78%). Among gram negative isolates 93% were sensitive to Colistin, 63% to Gentamicin & 54% to Levofloxacin.

Conclusion: Present study indicated that gram positive species especially CONS continue to be the predominant causative organism in both EOS and LOS and followed by Acinetobacter and E. coli in gram negative species.

Keywords: Neonatal sepsis, Early onset sepsis (EOS), Late onset sepsis(LOS), Coagulase-negative Staphylococci (CONS), culture isolates, antimicrobial sensitivity.

Introduction:

Sepsis is one of the leading causes of neonatal death in Bangladesh. Neonatal sepsis is defined as a disseminated disease with positive blood culture during the first month of life.¹ Neonatal sepsis considered to be an important cause of neonatal mortality and is more common in developing countries compared with developed countries.^{1,2} Children face the highest risk of dying in their first month of life, at a global rate of 19 deaths per 1,000 live births. Globally, 2.6 million children died in the first month of life, approximately

7,000 newborn deaths every day and about 98% of which occur in developing countries, particularly Asia and Africa.^{3,4} These neonatal deaths are attributed principally to infection (36%, which include sepsis/pneumonia, tetanus and diarrhea), birth asphyxia (23%) and consequence of prematurity & low birth weight (28%) and account for nearly 80% of total death in this age group. There is some variation between countries depending on their care configurations.^{3,4} Neonatal sepsis remains as an important cause of morbidity and mortality among infants in developing countries accounting for 30-50% of total deaths per year.⁵ The incidence of neonatal sepsis depends on geographic area and may vary from country to country as well as within the same country. In developing countries, neonatal mortality resulting from all causes of neonatal sepsis is about 34 per 1000 live birth, occurring mainly in the first week of life: whilst it is 5 per 1000 live birth in developed country.⁶ According to Bangladesh Demographic and Health Statistics (BDHS)-2017 Neonatal mortality rate (NMR) in

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Bangladesh is 30/ 1000 live birth. Global Infant mortality rate (IMR) is 31/1000 live birth, out of them about 70% of death occur neonatal period and global rate 19/1000 livebirth.⁷ Neonatal sepsis has been classified as either early onset (birth to 7 days of age) or late onset sepsis (8 to 28 days) i.e. infections occurring before and after one week of life.⁸ The reported incidence of neonatal sepsis varies from 7 to 38 per 1000 live birth in Asia⁹, from 6.5 to 23 per 1000 live birth in Africa¹⁰ and from 3.5 to 8.9 per 1000 live birth in South America and the Caribbean.^{11,12} By comparison, rates reported in the United States and Australia range from 6-9 per 1000 live birth^{13,14} and in Europe 0.3-3% per 1000 live birth.¹⁵ In most developing countries, gram negative bacteria remain the major cause of neonatal sepsis.^{16,17} These organisms developed increased drug resistance over the last two decades.¹⁸ On the other hand Group B Streptococcus (GBS) has been the most frequent causes of neonatal sepsis in developed countries, responsible for high mortality and morbidity.¹⁹ Rapidly changing antibiotic sensitivity pattern of bacterial agent causing neonatal sepsis, making its management more difficult for the health care providers.²⁰ Therefore knowledge of the pattern of bacterial isolates and their antimicrobial susceptibility is useful for treating patients with appropriate antibiotics. Although an extensive research is available worldwide^{18,21} but a few reports are available on neonatal sepsis in Bangladesh. The present study was undertaken to find out the positivity rate of neonatal sepsis and identify the bacterial isolates responsible for EOS and LOS and their antibiotic sensitivity pattern that were investigated for rule out sepsis.

Materials and Methods:

It was a prospective observational single center study. A total of 1000 neonates were investigated to rule out sepsis admitted in level-III NICU at Ad-din Medical College Hospital over a period of 9 month (January to September 2018). within 28 days of birth with a fulfilling the following admission criteria: 1. Gestational age less than 34 weeks, 2. Birth weight less than 1.8kg, 3. Unwell/sick Neonates e.g. respiratory distress, suspected sepsis, requires oxygen supplementation, convulsion, etc, 4. After prolonged resuscitation, 5. Neonates need mechanical ventilation, 6. Severe (Non lethal) congenital anomalies, 7. Any neonates requiring surgery, 8. Neonates with cord pH less than 7.0 and metabolic acidosis in early neonatal arterial blood sample (pH < 7.20 and base deficit e"

12mmol/L) within first hour of birth irrespective of gestation, 9. Hypoglycemia (if persistent despite oral feed or if <1.1mmol/L). Exclusion criteria included: 1. Newborns with lethal congenital anomalies, 2. Hyperbilirubinemia requiring intensive phototherapy, 3. Postnatal age >28days, and 4. Neonates held in a place of safety as result of child protection proceeding. Written informed consent was obtained from their parents and was investigated for bacterial etiologic agents. Demographic, clinical and other relevant data were obtained by attending pediatrician and were transferred to the questionnaire prepared for this study. Studied neonates were divided into two groups as early onset (from birth to 7 days old) and late onset (from 8 to 28 days old) sepsis. Neonates were also classified into normal birth weight (birth weight >2500gm) and low birth weight (birth weight <2500gm) and also into those with term (gestational age >37 - <42 completed weeks) and preterm (gestational age <37 completed weeks). Blood culture, chest x-ray and laboratory tests including complete blood count (CBC), CRP, blood sugar (BS) and electrolytes were performed for all subjects. Sample for blood culture was sent. An area of approximately 5 cm over the venipuncture site was disinfected with 70% alcohol followed by application of povidine iodine in concentric circles over the site and allowed to dry for at least 1 minute. About 1-2 ml venous blood was drawn from the peripheral vein and then the blood was inoculated into a BD BACTEC Peds plus culture vials (40ml). The specimens were transported immediately to microbiological laboratory of Ad-din Medical College Hospital and the test were carried out by BD BACTEC automated blood culture system & incubated for 120 hours in 37°C and were daily checked for evidence of bacterial growth. For positive cultures, subcultures were made solid media (Blood agar and McConkey agar) and were incubated in 37°C for 24 to 48 hours. The grown bacteria were identified by colony morphology, gram stain and biochemical tests. Diagnostic microbiology cultures which did not yield any growth following subcultures were reported negative at the end of 5 days. Antimicrobial susceptibility testing was done for all blood culture isolates according to the criteria of the National Committee for Clinical Laboratory Standards by disk diffusion method.

Results:

A Total 1000 neonates were investigated to rule out sepsis and 54 neonates (5.4%) were found positive on blood culture. Early and late onset sepsis were found in 70.37% (n=38) and 29.63 % (n=16) of cases

respectively (Table-I). Out of 38 isolates in EOS, gram positive contributed 71.05% (n=27) and gram negative 28.95% (n=11) and in LOS we found 16 isolates, of which gram positive 81.25% (n=13) and gram negative 18.75% (n=3) of cases respectively. CONS (68.42%) was the commonest and followed by Acinetobacter (18.42%) in EOS. In LOS, CONS (75%) is the most prevalent organism. CONS was common culprit for both early (68.42%) and late (75%) onset sepsis (Table-II).

Table I

Bacterial isolates based on sepsis onset (n=54)

Neonatal Sepsis	Total culture positive
EOS	38 (70.37%)
LOS	16 (29.63%)

EOS=Early onset sepsis, LOS=Late onset sepsis
 Out of 54 isolates, the gram positive bacteria accounted for 74% (n=40) and gram negative 26% (n=14) of the total isolates. Among the gram positive, CONS 95 % (n=38) is the commonest isolate, other

gm positive are Staphylococcus 2.5% (n=1) and streptococcus viridans 2.5% (n=1). In gram negative isolates Acinetobacter 50% (n=7) is the most prevalent bacteria followed by E.coli 28.57%(n=4), others are Enterobacter 14.29% (n=2), Klebsiella 7.14% (n=1).

Based on the results from susceptibility testing gm positive organism had highly sensitivity to Vancomycin 83% (n=33), Linezolid 78% (n=31) and Gentamicin 73% (n=29). Moderate sensitivity to Levofloxacin 55%(n=22). Less sensitivity to Ampicilin 35%(n=14), Cefotaxime 35%(n=14), Oxacillin 33%(n=13) and Ciprofloxacin 28%(n=11). And remarkably lower sensitivity to Meropenem 18%(n=7), Amoxyclave 18% (n=7) and 100% resistant to Amikacin. CONS showed 100% resistant to Amikacin (Table-III).

All gram negative bacteria were highly sensitive to Colistin 93% (n=13) and moderate sensitive to Amikacin 64% (n=9), Ciprofloxacin 50% (n=7) and Levofloxacin 50% (n=7). Less sensitive to Gentamicin 36%(n=5) and Meropenem/Imipenem 43% (n=6). Most common gram negative organism was Acinetobacter 50% (n=7) and most sensitive to

Table II

Organisms Isolated (n=54)

Bacterial isolates	Type of sepsis		Total (%) (n=54)
	EOS (n=38)	LOS (n=16)	
Gram positive isolates	27 (71.05%)	13 (81.25%)	40 (74%)
CONS	26 (68.42%)	12 (75%)	38 (70.37%)
Staphylococcus aureus	—	01 (6.25%)	01 (1.85%)
Streptococcus viridans	01 (2.63%)	—	01 (1.85%)
Gram negative isolates	11 (28.95%)	03 (18.75%)	14 (26%)
Acinetobacter	07 (18.42%)	—	7 (12.97%)
E.coli	03 (7.9%)	01(6.25%)	4 (7.41%)
Enterobacter	01 (2.63%)	01 (6.25%)	2 (3.70%)
Klebsiella	—	01 (6.255%)	1(1.85%)
Total	38 (100%)	16 (100%)	54 (100%)

Table III

Antimicrobial sensitivity pattern of gram positive isolate (n=40)

	Amp	Genta	Merop	Linezo	Vanco	Amxcl	Oxacil	Cipro	Levo	Cefotax	Amk
CONS (38)	13(34%)	29(76 %)	6(16%)	30(79%)	31(82%)	7(18%)	13(34%)	10(26%)	21(55%)	13(34%)	0
Staph. Aureus (1)	0	0	1(100%)	1(100%)	1(100%)	0	0	0	0	0	0
Strepto. Viridians (1)	1(100%)	0	0	0	1(100%)	0	0	1 (100%)	1 (100%)	1(100%)	0
Total(40)	14(35%)	29(73%)	7(18%)	31(78%)	33(83%)	7(18%)	13(33%)	11(28%)	22 (55%)	14(35%)	0

CONS: Coagulase negative staphylococcus aureus, Amp: Ampicillin, Genta: Gentamicin, Amk: Amikacin, Merop:Meropenem, Linezo: Linezolid, Vanco:Vancomycin, Amxcl: Amoxyclav, Oxa: Oxacillin, Cipro: Ciprofloxacin, Levo: Levofloxacin, Cefotax: Cefotaxime.

Table-IV
Antimicrobial sensitivity pattern of gram negative organism (n=14)

Gm (-)ve organism	Amp	Genta	Amk	Cipro	Merop	Amxcl	Levo	Pip	Col	cefotax
Acinetobacter (7)	0	0	2 (29%)	2 (29%)	2 (29%)	2 (29%)	2 (29%)	0	6 (86%)	0
E. Coli, (4)	3 (75%)	4 (100%)	4 (100%)	4 (100%)	1 (25%)	1 (25%)	3 (75%)	0	4 (100%)	3 (75%)
Enterobacter, (2)	0	1 (50%)	2 (100%)	1 (50%)	2 (100%)	0	2 (100%)	1 (50%)	2 (100%)	0
Klebsiella, (1)	0	0	1 (100%)	0	1	0	0	1(100%)	1 (100%)	0
Total= 14	3 (21%)	5 (36%)	9 (64%)	7 (50%)	6 (43%)	3 (21%)	7 (50%)	2 (14%)	13 (93%)	3 (21%)

Amp:Ampicillin, Genta:Gentamicin, Amk:Amikacin, Merop:Meropenem, Amxcl:Amoxyclave, Cipro:Ciprofloxacin, Levo:Levofloxacin, Cefotax:Cefotaxime. PIP:Piperacillin, Col:Colistin.

Colistin 86%(n=6) and less sensitive to Imipenem/ Meropenem 29%(n=2), Amikacin 29% (n=2) and Ciprofloxacin/ Levofloxacin 29% (n=2) and resistant to Ampicillin, Gentamicin, Cefotaxime and Piperacillin+tazobactam. Second common gram negative organism was E. coli 28.57% (n=4), all (100%) were sensitive to Gentamicin, Amikacin, Colistin and 75% (n=3) sensitive to Ampicillin, Cefotaxime (Table-IV).

Discussions:

In this study, prevalence of documented neonatal sepsis with positive culture was 5.4%. This is low compared to about 20% yield reported by Baltimore²² and Gladstone²³ but near (8.7%) to Jahan N study.²⁴ In the present investigation 70.38% and 29.62% neonates presented with early onset sepsis (EOS) and late onset sepsis (LOS) respectively. We found that EOS was more common than LOS, which is in agreement with the reports from other developing countries e.g. in Iran² (77.5% vs. 22.5%) and in study of Bangladesh, Haque ZSM (74.86% vs 25.14%) et al.²⁴ and Rasul CH²⁵ (70.7 vs 29.3%) but in contrast with reports from Saudi Arabia (39% vs 61%)²⁶ and Pakistan (42% vs 58%),²⁷ where late onset sepsis is more common. Isolation of gram positive and gram negative bacteria in this study was 74% and 26%. This study finding is not similar to that of other studies which shows that gram negative bacteria were the commonest cause of neonatal sepsis.^{2,24,28,29} This was similar to other studies which shows gram positive bacteria are the common cause of neonatal sepsis,^{12,16,30} while another studies showed, the frequency of isolation of gram positive and gram negative bacteria were equal.²⁶ In 1998 Ahmed NU etal.²⁸ and Gary L. Darmstadt et al.³¹ shows blood culture positivity was lower in those with early (26%, 12/46) compared to late-onset (45%, 18/40) disease (P < 0.05). Of the 30 organisms isolated, nearly three-

fourths (73%, 22/30) were gram-negative bacilli; 8(27%) were gram-positive. *Escherichia coli* was the most common organism (30%, 9/30), followed by Klebsiella pneumoniae (23%, 7/30) and Staphylococcus aureus (17%, 5/30). Rakibul Islam Q et al.³² showed among the enrolled 100 clinical septicemia in neonates 68(68%) were EOS and 32(32%) LOS. Gram-negative isolates were 22 (70.97%) and gram-positive 9 (29.03%). Klebsiella pneumonia was the most common (41.9%), followed by staphylococcus aureus (29%) and E. coli (19.4%) among the isolates. In 2008-2009 Begum S.et al.³³ found LOS was more common than EOS (64.4% vs. 35.6%). 98.5% sepsis was caused by Gram negative organism, in which 52.3% caused by Klebsiella. Second most common organism was Enterobacter (21.5%). Other organisms were Acinetobacter (10.8%), Pseudomonas (7.7%), Serratia (3.1%), and Citrobacter (3.1%). Gram positive organism (Staphylococcus) was found in only one neonate. Coagulase Negative Staphylococcus (CONS) was the most common isolates (70.37%) causing neonatal sepsis followed by Acinetobacter (12.97%) isolated in the study. The possible explanation for a higher frequency of EOS in the study might be the referral of more preterm labors and preterm, sick newborns from other centre or outside of Dhaka city to our centre with history of poor antenatal care (ANC), and delivered by unskilled birth attendant. Gram positive organism are more as the babies comes from community where gram positive organism are common then hospital acquired infection where gram negative are more. This study is similar to the study which shows gram positive bacteria such as Staphylococcus Aureus and Group B Streptococcus (GBS) were found to be the most common causes of neonatal sepsis.^{12,30} But this study result is opposite to studies of most developing countries,^{24,34} where showed gram negative organisms were the common

cause of neonatal sepsis.^{24,30} Studies from different countries reported CONS as predominant organisms in LOS.^{35,36} In the present study, CONS showed resistant to Amikacin (100%), lower sensitivity to Meropenem (16%) and Amoxycylave (18%) in comparison to Vancomycin (82%) Linezolid (79%) and Gentamicin (76%); moderate sensitive to Levofloxacin (55%) and less sensitive to Ampicillin (34%), Cefotaxime (34%), Oxacillin (34%) and Ciprofloxacin (26%). These findings similar to study Haque ZSM.³⁷ All gram negative bacteria were highly sensitive to Colistin (93%); moderate sensitive to Amikacin (64%), Ciprofloxacin/Levofloxacin (50%) and less sensitive to Imipenem/Meropenem (43%) and Gentamicin (36%). Higher susceptibility to Amikacin and Colistin was reported by Haque ZSM.³⁷ and Ramesh.³⁸ Low sensitivity to Ampicillin and Cefotaxime is similar to many earlier studies.^{13,37,39,40}

In the present study 54%-83% organisms was sensitive to Levofloxacin- Gentamicin or Levofloxacin-Vancomycin. So these can be initial combination before blood culture reports available. Linezolid also had good sensitivity but as it had gram positive coverage, it cannot be used in initial combination. Ampicillin and Gentamicin had a moderate sensitivity, so that can be used as initial antibiotic combination. However these results are limited to study cohorts and every center should have idea about their own bacterial sensitivity pattern. Different neonatal intensive care unit (NICU) shows different epidemiological data for neonatal sepsis. So collection of up-to-date & site specific data is mandatory for appropriate use of antibiotics

Conclusion:

Gram positive organisms especially CONS continue to be the predominant causative organism in both EOS and LOS and followed by Acenitobacter and E. coli in gram negative species. In neonatal sepsis initial choice should be Ampicillin and Gentamicin /Levofloxacin and Gentamicin in EOS and Vancomycin in combination with Amikacin or Colistin in LOS. Continuous survey on the organisms responsible for neonatal sepsis and their antimicrobial sensitivity pattern should carry on.

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