# Original Article

# Distribution of Microorganisms in Neonatal Sepsis and Possible Outbreak of Enterobacter spp. in Neonatal Intensive Care Unit

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## Abstract

***Background:*** *Neonatal sepsis is one of the leading causes of neonatal mortality and morbidity globally, more in developing countries. Frequent monitoring of changing pattern of pathogens causing neonatal sepsis is mandatory for effective treatment.* ***Objectives:*** *This study was done to isolate and identify different organisms of sepsis and to compare different types of organisms between early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS).* ***Materials and Methods:*** *This cross sectional descriptive study was conducted in Department of Microbiology in collaboration with Department of Neonatology, (DMCH) Dhaka. Blood sample was collected from 106 clinically suspected septicemic neonates and isolation and identification of organism was done by automated blood culture and standard microbiological protocol. Data was collected from attendants by filling a predesigned questionnaire.* ***Results:*** *Among 106 samples, 76 (71.69%) were blood-culture positive. Prevalence of (LONS) was higher 42 (55.26%) in comparison to (EONS) 34 (44.74%). Male neonates were affected more 42 (55.26%) than female 34 (44.74%). Among the isolated organisms, Enterobacter spp. was the predominant organism 20 (26.31%) followed by Klebsiella pneumoniae 18 (23.68%) and Candida spp. 12 (15.79%).* ***Conclusion:*** *Gram-negative organisms play the leading role for causing neonatal sepsis and Enterobacter outbreak should be concerned. Therefore, regular surveillance of organism profile causing neonatal sepsis is of utmost necessity.*

***Keywords:*** *Neonatal sepsis, Early-onset neonatal sepsis (EONS), Late-onset neonatal sepsis (LONS), Enterobacter spp.*

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## Introduction

Neonatal period, first 28 days of life is a crucial time when the newborn has to adopt to a new environment. During this time, a neonate is susceptible to many problems ranging from mild morbidity to life threatening condition.[1] Each year, approximately three million children die in the first 28 days after birth.[2] The leading cause of death globally are preterm birth (35.7%), intrapartum complications (23.4%) and sepsis (15.6%).[3]

Systemic illness caused by microbial invasion of normally sterile parts of the body is referred to as sepsis.[4] Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life.[5] The condition may be defined both clinically and/or microbiologically, by positive blood and/or cerebrospinal fluid cultures.[6]

Neonatal sepsis is classified in two groups: EONS and LONS.[6] EONS hasbeen variably defined based on the age at onset, with bacteremia or bacterial meningitis occurring at <72 hrs in infants hospitalized in the neonatal intensive care unit

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(NICU), versus <7 days in term infants.[7-9] In preterm infants, EONS is most consistently defined as occurring in the first 3 days of life and is caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery.[8] LONS is sepsis occurring after 72 hrs in NICU infants and 7 days of life in term infants, has been variably defined as occurring up to the age of < 90 or 120 days, and may be caused by vertically or horizontally acquired pathogens.[7,8,10-12]

Many risk factors are found to influence the development of neonatal sepsis. Some are maternal factors and some are neonatal factors. Among the maternal factors, the maternal intrapartum fever, prolonged labor, unclean vaginal examination (UVE), foul smelling liquor, young mother (<20 y), and poor income group are much associated with the occurance of sepsis. Among the neonatal factors, prematurity, resuscitation at birth and low APGAR score carry the significant risk of developing sepsis.[13]

Neonatologists remain constantly baffled by the changing patterns of microbial flora, making neonatal septicemia a difficult problem to tackle.[14] A number of organisms are associated with neonatal sepsis and bacterial pathogens may vary from one country to another and within a country from one hospital or region to another and even vary at different times within the same place.[15-17]

Neonatal surveillance in developed countries generally identifies Group B Streptococcus (GBS) and Esch. coli as the dominant EONS pathogens and coagulase negative Staphylococci (CONS) as the dominant LONS pathogen followed by GBS and Staph. aureus.[18] In developing countries, overall gram-negative organisms are more common and are mainly represented by Klebsiella spp., Esch. coli and Pseudomonas spp. Of the gram-positive organisms, Staph. aureus, CONS, Streptococcus pneumoniae, Streptococcus pyogenes and Candida spp. are most commonly isolated.[18]

In Bangladesh, the current Neonatal Mortality Rate is 28 per 1000 live births.[19] The overall sepsis rate estimated is 7.45%.[20] Increase in mortality of 7.6% was observed for every hour delay in administrations of antimicrobials in case of septic shock.[21] Therefore, this study was designed to detect the microbial profile in neonatal sepsis in NICU by automated blood culture and different biochemical tests.

## Materials and Methods

This cross-sectional descriptive study was conducted in Department of Microbiology, in collaboration with Department of Neonatology, DMCH, Dhaka during the period from January 2016 to December 2016 after approval of the protocol by Research Review Committee of the Department of Microbiology and Ethical Review Committee of Dhaka Medical College.

A total 106 neonates of either sex of age 0-28 days, both in-born and out-born, admitted in NICU of DMCH with suspected clinical features of sepsis at admission or developing such features afterwards when admitted for other indications, irrespective of antibiotic intake were included. Neonates with congenital anomalies, acute bilirubin encephalopathy, perinatal asphyxia, meconium aspiration syndrome, history of prolonged rupture of membrane and prolonged labor of mother were excluded from this study.
After proper explanation regarding the nature of the study, written consent was taken from legal guardian of neonates. Detailed history was obtained from the mother or the attendants by predesigned questionnaire for filling the history sheet to select the suspected septicemic neonates.

With all aseptic precaution, after disinfecting the selected venipuncture site with 10% povidone iodine followed by 70% alcohol, a single sample of 2 ml blood was collected and inoculated into BacT/ALERT PF Plus bottle (bioMerieux, Inc, Durham, North Carolina) for isolation and identification of organism by automated blood culture. At first the needle which was used for venipuncture was discarded and was replaced by a new sterile needle. After removing the cap, the top of the BacT/ALERT PF Plus bottle was disinfected by 70% alcohol and was allowed to air dry. Then 2 ml of blood was inoculated into the bottle by piercing the rubber top of the bottle. The BacT/ALERT PF Plus bottle was then agitated gently to mix the blood with the media. Each bottle was labelled with the appropriate patient information- sample number, patient name, date and time of collection, registration number. Then bottle was taken to Microbiology laboratory of DMCH without delay and bottle was processed using the BacT/ ALERT 3D 60 Microbial Detection System (bioMerieux, Inc, Durham, North Carolina). BacT/ ALERT PF Plus bottles contain 30ml of complex medium and 1.6g adsorbent polymeric beads. Bottles that did not become positive were discarded from the system after 7 days.

After disinfecting top of the positive vial with 70% alcohol, a small volume of blood was aspirated with the help of a sterile disposable syringe and then sub-culture was done on blood agar, MacConkey agar, and Chocolate agar media by dispensing 2-3 drops. The blood agar and MacConkey agar plates were incubated aerobically at 370C and the chocolate agar plates were incubated in a candle extinction jar at 370C. The culture plates were examined after 24 hours for microbial growth, if there was no growth then plates were incubated again and were examined after 24 hours. If there was growth of microbial colony then all the organisms were identified by colony morphology, hemolytic criteria, pigment production, different biochemical tests and staining character as per standard techniques. For each positive culture, a record of the vial and the initial time of detection were recorded. When the microbial growth had been confirmed then the bottles and the plates were discarded according to the safety procedure. If no growth obtained the plates were discarded after 3 days in the same way.

Data analysis was done by using "Microsoft Office Excel 2013" program and statistical significance was compared using the z-test of proportion. Significance was assigned a p value of <0.05.

## Results

Among one hundred and six septicemic neonates, 76 (71.69%) were found blood culture positive and 30 (28.31%) were found blood culture negative (Figure 1).

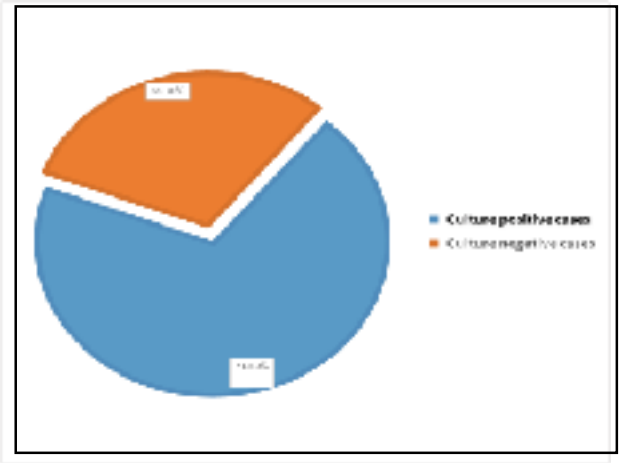

**Figure 1:** The results of blood culture among suspected septicemic neonates (N = 106).

Among 76 culture positive cases, bacteria were isolated from 64 (84.21%) cases and Candida spp. were isolated from 12 (15.79%) cases (Table I).

**Table I:** Distribution of the isolated organisms among blood culture positive cases (N=76).

| Isolated organisms | Positive n (%) |
|---|---|
| Bacteria | 64 (84.21) |
| *Candida* spp. | 12 (15.79) |
| **Total** | **76 (100.00)** |

Out of 76 culture positive cases, 42 were male, 34 were female and EONS was found in 34 cases whereas LONS was found in 42 cases. Among 34 EONS cases, 10 (62.5%) were term male, 6 (37.5%) were term female and 8 (44.44%) were preterm male, 10 (55.56%) were preterm female. Ten (55.56%) term male, 8 (44.44%) term female and 14 (58.33%) preterm male, 10 (41.67%) preterm female was found among 42 LONS cases (Table II).

**Table II:** Sex distribution of EONS and LONS cases in relation to term and preterm delivered babies (N = 76).

| Sex | EONS (N = 34) | | LONS (N = 42) | |
|---|---|---|---|---|
| | Term n (%) | Preterm n (%) | Term n(%) | Preterm n (%) |
| Male (n=42) | 10 (62.5) | 8 (44.44) | 10 (55.56) | 14 (58.33) |
| Female (n=34) | 6 (37.5) | 10 (55.56) | 8 (44.44) | 10 (41.67) |
| **Total** | **16 (47.06)** | **18 (52. 94)** | **18 (42.86)** | **24 (57.14)** |

Note: EONS = Early-onset Neonatal Sepsis
LONS = Late-onset Neonatal Sepsis
N = Total number
n = Number of positive cases

Out of 34 (44.74%) EONS cases, Enterobacter spp. was found to be the predominant organism which was 10 (29.41%) followed by Klebsiella pneumoniae 8 (23.53%). The other organisms isolated from EONS cases were Pseudomonas aeruginosa 4 (11.76%), Staphylococcus aureus 4 (11.76%), CONS 2 (5.88%), GBS 2 (5.88%) and Candida spp. 4(11.76%). Ten (23.81%) Enterobacter spp. and 10 (23.81%) Klebsiellapneumoniae were isolated among 42 (55.26%) LONS cases followed by 4 (9.52%) Pseudomonas aeruginosa, 4 (9.52%) Acinetobacter baumannii, 2 (4.76%) CONS, 2 (4.76%) Micrococcus spp. and 8 (19.05%) Candida spp. (Table III).

**Table III:** Distribution of organisms in EONS and LONS (N=76).

| Microorganisms | EONS n (%) | LONS n (%) | Total n (%) |
|---|---|---|---|
| Enterobacter spp. | 0 (29.41) | 10 (23.81) | 20 (26.31) |
| Klebsiella pneumoniae | 8 (23.53) | 10 (23.81) | 18 (23.68) |
| Candida spp. | 4 (11.76) | 8 (19.05) | 12 (15.79) |
| Pseudomonas aeruginosa | 4 (11.76) | 4 (9.52) | 8 (10.53) |
| Acinetobacter baumannii | 0 (0.0) | 4 (9.52) | 4 (5.26) |
| Staphylococcus aureus | 4 (11.76) | 0 (0.0) | 4 (5.26) |
| CONS | 2 (5.88) | 2 (4.76) | 4 (5.26) |
| GBS | 2 (5.88) | 0 (0.0) | 2 (2.63) |
| Citrobacter freundii | 0 (0.0) | 2 (4.76) | 2 (2.63) |
| Micrococcus spp. | 0 (0.0) | 2 (4.76) | 2 |

CONS= Coagulase Negative Staphylococcus
GBS= Group B Streptococcus

## Discussion

Neonatal sepsis still remains a diagnostic and treatment challenge for the neonatal health care providers. The spectrum of organisms responsible for neonatal sepsis change over time and also varies from region to region. The study of bacteriological profile plays a very important role for effective management of neonatal sepsis. In this study, 71.69% of cases were blood culture positive out of 106 cases. In previous studies, the reported prevalence of neonatal sepsis by authors in Bangladesh was much lower such as 7.45%, 15.8%, 13% and 48.75%.[1,20,22,23] Rahman[24] reported 48.75% prevalence of neonatal sepsis in NICU of DMCH in 2015. Lower isolation rates were reported in Iran (6.6%), Libya (5.9%) and Bahrain (4.2%).[25,26,27] The relatively higher isolation rates were reported by Al-Shamahy et al.[28] (57%) from Yemen, Awrangzeb and Hameed[15] (59.82%) from Pakistan, Chelliah etal.[29] (60.4%) and Misra et al.[30] (65.21%) from India and Awoniyi et al.[31] (78%) from Nigeria. The higher isolation rate in this study than the previous studies in Bangladesh might be due to the fact that automated blood culture system was used in this study (FAN method) but other researchers used conventional blood culture method. Isolation of 26.31% of Enterobacter spp. as a causative organism of neonatal sepsis is a striking feature of this study and this also may have contributed to the high prevalence rate. Moreover, overcrowding in NICU of DMCH and high patient to healthcare provider ratio may be another contributing factor for high isolation rate. However, the incidence of neonatal sepsis may vary from country to country as well as, within the same country from one institution to another and even year to year in the same institution.[32,33]

According to this study, male neonates (55.26%) suffered more from neonatal sepsis than female neonates (44.74%) and the blood culture positive male to female ratio was 1.2:1. These findings correspond to the male to female ratio of 1.3:1 reported by Eman et al.[34] Though the difference in male to female predominance in this study was not statistically significant (P>0.05), male predominance was found in almost all the studies of neonatal sepsis.[14,35,36] Increased male septicemic neonates in this study may be due to gender biasness for hospital care in Bangladesh like other developing countries. Moreover, males are more prone to infection as genetic loci on the X chromosome. Presence of one X chromosome in the male baby confers less immunological protection compared to the female counterpart.[37,38]

LONS (55.26%) was found more prevalent than EONS (44.74%) in this study. This finding is almost similar to the reports from other countries such as, 55.8% LONS vs 44.2% EONS in Egypt, 58% LONS vs 42% EONS in Pakistan.[34,39] In contrast, more EONS were reported in some studies such as, 22.5% LONS vs 77.5% EONS in Iran.[25] The possible explanation for higher frequency of LONS in this study might be attributed to the increasing use of life supporting measures and improved survival of sick neonates, as well as delay discharge policy in DMCH, failure of early enteral feeding with breast milk and poor hygienic policies may have some role in rise of LONS due to nosocomial infections. Genetic factors, such as the polymorphism in immunity associated genes may also be implicated in neonatal susceptibility to LONS.[40]

It is evident from this study that neonatal sepsis occurs more in case of preterm babies than term babies, such as, 57.14% preterm vs 42.86% term in case of LONS and 52.94% preterm vs 47.06% term in case of EONS were reported. This finding agrees with the previous study conducted by Rahman[24] who reported 67.71% preterm vs 39.42% term in NICU of DMCH in 2015. This is also similar to the findings documented by other studies.[20,23,29,32] Serum immunoglobulin (Ig) level is significantly lower in preterm babies compared to term babies. Trans-placental passage of serum IgG from mother to fetus starts at about 12$^{th}$ weeks of gestation and most of the passage occurs after 32 weeks to term.[41] Therefore, IgG level is directly proportional to gestational age. These preterm babies are lack of first line defense than term babies, therefore, they are more susceptible to infection.

In this study, Candida spp. accounted for 15.79% of cases and bacteria for 84.21% cases of neonatal sepsis and Candida spp. was the 3$^{rd}$ most common pathogen responsible for total neonatal sepsis cases. Rahman24, in his study in NICU of DMCH also reported Candida spp. as the 3rd most common pathogen and was responsible for 16.98% of the total cases which is almost similar to this study. This finding is in agreement with some other studies from different countries.[42,43,44,45] To this date, in spite of isolating Candida spp. from blood of suspected neonatal sepsis cases, antifungal drug is not used in our country as because Candida spp. is thought to be the contaminant.

Enterobacter spp. was the predominant (26.31%) and Klebsiellapneumoniae was the 2nd most common (23.68%) organisms among the isolated bacteria found in this study. No other studies in this country reported Enterobacter spp. as the predominant organism to cause neonatal sepsis. In the previous study conducted by Rahman[24] in NICU of DMCH, Klebsiellapneumoniae (24.53%) was the predominant followed by Staphylococcus aureus (22.64%). In Bangladesh, Begum et al.[46] reported 52.3% Klebsiella spp. as the predominant pathogen followed by 20% Enterobacter spp. in 2012 and in 2013, Begum et al[22] reported 42.04% CONS followed by 27.27% Acinetobacter spp. as most common pathogen and 3.04% of Enterobacter spp. was reported in that study. In India, Das et al.[47] reported Escherechiacoli (25.55%) followed by Klebsiella spp. (24.44%) and in Nepal, Shrestha et al.[48] reported Klebsiella pneumoniae (28.72%) followed by Staph. aureus (18.1%) as the predominant organism. 22.5% Enterobacter cloacae and 78.1% Enterobacter spp. were reported as predominant pathogen of neonatal sepsis in Egypt and Iran respectively.[49,50] This striking high frequency of Enterobacter spp. reported in this study may be due to an

outbreak of neonatal sepsis by this bacteria having similar antimicrobial susceptibility. In India, Antony[51] reported an outbreak of neonatal sepsis by Enterobacter cloacae. Outbreak of Enterobacter spp. in NICU is also evident from studies of researchers in other countries as well.[52,53] Contaminated water source in NICU, contaminated TPN (Total per-enteral nutrition) solution or contamination by baby's attendants could be the possible source of Enterobacter outbreak.

## Conclusion

In this study, Entrerobacter spp. were the predominant pathogen and were responsible for 26.31% cases of neonatal sepsis. The high prevalence suggests that there might be an outbreak of Enterobacter spp. in NICU of DMCH. Extreme measures should be taken regarding eradication of the source of Enterobacter spp., hygiene of health-care workers and strict monitoring of visitors.

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