Original Research

A Case–Control Study On the Etiology And Risk Factors Related To Early-Onset Neonatal Sepsis in Western Region of Uttar Pradesh, India

Dr. Ranjana Yadav[1], Dr. Anand Narain Prasad[2], Dr. Anjum Parwez[3], Dr. Neerja Katiyar[4]

[1]Assistant Professor, Department of Paediatrics, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India
[2]Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India
[3]Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India
[4]Assistant Professor, Department of Obstetrics & Gyanecology, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India

Corresponding Author
Dr. Ranjana Yadav
Assistant Professor, Department of Paediatrics, Rama Medical College, Hospital & Research Centre, Hapur, U.P., India.
Email ID: ranjanaayadav@yahoo.co.in

Received: 02 January, 2016 Accepted: 20 March, 2016 Published: 25 March, 2016

ABSTRACT

Background: Neonatal sepsis constitutes a significant public health challenge on a global scale. It represents a significant contributor to neonatal mortality and morbidity globally. Neonatal mortality rates are elevated in developing nations, where the prevalence and etiology of neonatal sepsis remain largely unexplored. Neonatal sepsis constitutes a primary contributor to neonatal mortality in India.

Aim: This study aimed to determine the risk factors and microorganisms associated to early-onset neonatal sepsis (EONS) in a tertiary healthcare center situated in western region of Uttar Pradesh, India.

Materials and Methods: It was a case–control study performed in the neonatal unit of Rama Medical College, Hospital & Research Centre, Hapur, Uttar Pradesh, from January 2015 to December 2015. All neonates admitted to the neonatal intensive care unit (NICU) within the first 72 hours of life comprised the study population. Neonates identified as EONS through clinical and laboratory criteria were categorized as cases, while those without an EONS diagnosis were classified as controls. Maternal and neonatal data, along with laboratory parameters, were gathered and scrutinized. The bivariate logistic regression was employed for the identification of risk factors.

Result: Bivariate logistic regression revealed that mothers over 35 years had a higher risk of Early Onset Sepsis (p=0.0151) than mothers under 35 year of age. Maternal UTI in pregnancy strongly risked EOS (p<0. 05). In summary, maternal UTI, age ≥35, PROM, and no antenatal care were key EOS risk factors in this study. Survival rates were lower in cases (77.6%) than in controls (92.5%). Mortality was higher in cases (22.4%) than controls (7.5%). Survival was worse in the case group than the control group. Among gram-negative organisms, *E. coli* is a common cause of infections and showed high resistant to ampicillin (88.9%) and cefoxitin (66.7%). Similarly, *Klebsiella* showed high resistant to ampicillin (80.9%) and cefoxitin (71.4%). *Pseudomonas* was 100% resistant to piperacillin and 66.7% to both imipenem and ciprofloxacin. *Enterococcus* was high resistance to ampicillin (80.8%) among gram-positive organisms. 13 (52%) *S. aureus* were MRSA and out of 12 MSSA isolates, 8 (66.7%) resistant to penicillin.

Conclusion: Comprehensive and appropriate antenatal screening for the identification and management of maternal infections and high-risk pregnancies is advised to facilitate perinatal care of newborns, thereby mitigating morbidity and mortality associated with neonatal sepsis. The judicious utilization of antibiotics can effectively reduce the risk of developing antibiotic resistance.

Keywords: Antenatal screening, Neonate, Neonatal sepsis, NICU

INTRODUCTION

The neonatal period commences at birth and concludes 28 days thereafter. Consequently, due to perinatal and obstetric trauma, neonates may experience various health complications. Neonatal sepsis (NNS) is characterized as a systemic inflammatory response syndrome that varies from subclinical infection to severe or systemic manifestations resulting from bacteria, viruses, or fungi in neonates [1–4]. It is classified into two categories: early-onset neonatal sepsis (EONS), which develops within the initial 7 days of life as a result of microbial infections transmitted vertically from mother to child, and late-onset neonatal sepsis (LONS), which affects infants in the neonatal intensive care unit (NICU) from the 8th to the 28th day of life [3, 5, 6]. The clinical manifestations of early-onset neonatal sepsis (EONS) are ambiguous and inadequate for distinguishing newborns afflicted with this condition [7]. A blood culture report requires a minimum of 48 hours and has shown positive results in 25–45% of cases, with a heightened risk of false positive outcomes and reduced yield results following prenatal antibiotic use. In India, cultural testing facilities are lacking in the majority of district hospitals [8]. In this context, the anticipation and identification of neonatal sepsis are contingent upon culture-independent diagnostic methods and a risk factor scoring system [9]. The application of a risk factor-based approach to inform treatment decisions has been subject to discussion, particularly regarding cost-effectiveness [10, 11]. This strategy has demonstrated its efficacy in decreasing EONS-related mortality within high-income nations [12]. In resource-constrained environments where blood culture facilities are not available, the predictive risk factor model of EONS suggests that early diagnosis and appropriate management of EONS can result in reduced mortality [13]. The occurrence of elevated prevalence of EONS accompanied by the onset of sclerema within 72 hours of birth represents the predominant cause of mortality in this isolated tertiary healthcare facility. Consequently, the identification of risk factors and etiologies dominant in this geographical region has emerged as a critical imperative for enhancing neonatal care. In this perspective, the research was undertaken to identify the risk factors and pathogenesis of early-onset neonatal sepsis (EONS) in neonates born at a tertiary care facility in Uttar Pradesh, India. The data acquired can significantly contribute to risk stratification and the prompt prediction of EONS, facilitating informed diagnostic decisions and the commencement of appropriate treatment in resource-constrained environments such as remote healthcare facilities.

AIM: This study aimed to determine the risk factors and microorganisms associated to early-onset neonatal sepsis (EONS) in a tertiary healthcare center situated in western region of Uttar Pradesh, India.

MATERIALS AND METHODS

This is a prospective case–control study conducted within a tertiary neonatal care unit located in western region of Uttar Pradesh, India. The period of investigation, including data collection and analysis, extended from January 2015 to December 2015. The research has been endorsed by the Ethical Committee of Rama Medical College, Hospital & Research Centre, Hapur, U.P., India.

Inclusion criteria: All neonates born intramurally and admitted to the neonatal intensive care unit (NICU) within 72 hours of birth were included in the study.

Exclusion criteria: Neonates presenting with congenital anomalies, coupled with neonatal documentation and inadequate maternal, as well as a failure of the mother or caregiver to provide a comprehensive medical history, were excluded from the study.

The dependent variables encompass neonatal culture-positive sepsis (defined as the isolation of at least one organism) and resistance patterns, as well as the mortality or discharge of infants involved in the study. Maternal factors encompass age, delivery method, gravidity and parity, maternal fever, premature rupture of membranes (PROM), urinary tract infection (UTI), obstructed labor, and antenatal care (ANC) visits. Neonatal factors encompass birth weight—specifically, low birth weight (LBW) defined as a birth weight less than 2.5 kg or normal birth weight of 2.5 kg or more as well as the objective assessment score (APGAR score) and gestational age.

Case Group: The standardized Integrated Management of Neonatal and Childhood Illness (IMNCI) clinical presentation encompasses the existence of two or more of the following indicators: sustained fever (exceeding 37.5°C), tachypnea (respiratory rate exceeding 60), hypothermia (below 35.5°C) lasting for one hour, chest indrawing, grunting, convulsions, lethargy, poor feeding, irritability, and unconsciousness, in conjunction with two hematological criteria such as a total leukocyte count (TLC) more than 12,000 or less than 4,000 cells/mm^3, an absolute neutrophil count (ANC) less than 1,500 or more than than 7,500 cells/mm^3, a positive C-reactive protein (CRP), thrombocytopenia (platelets less than 150,000/mm^3), and hypoglycemia (random blood sugar; Random Blood Sugar <40 mg/dl). These criteria, along with a positive blood culture, serve as diagnostic indicators of neonatal sepsis [14].

Control Group: It encompasses healthy neonates diagnosed with non-sepsis conditions (not meeting the criteria of the Integrated Management of Neonatal and Childhood Illnesses - IMNCI).

Sample Size and Design: Both cases and controls were chosen via a simple random sampling method from neonates admitted to the NICU within 72 hours of birth. The sample size was determined using Epi Info software (version 3) with 80% statistical power, a 95% confidence interval, according to the Kelsey method. [15] The aggregate sample size comprised 268 participants, with 134 individuals designated as cases and 134 as controls.

Specimen collection: Two milliliters of blood were collected from a peripheral vein while adhering to appropriate aseptic techniques in a pediatric blood culture broth (20 ml) vial. It was placed in an automated incubator at 37°C for duration of 24 hours. If the culture exhibits growth, subcultured on blood or chocolate agar and incubated at 37 degrees Celsius for up to 96 hours; however, bottles that demonstrate negative results, indicating no growth, are further incubated for an additional five days before being deemed negative. The classification of bacterial species was conducted utilizing colony morphology, Gram staining, and biochemical tests. Drug susceptibility testing was conducted on Mueller–Hinton agar employing the disk diffusion method in accordance with the current Clinical Laboratory Standard Institute (CLSI) guideline.

Data collection: We secured written informed consent and collected pertinent maternal and neonatal data through interviews with the mother or caregiver and examination of medical records, utilizing a checklist and a structured data abstraction form. Admitted neonates were monitored until either their discharge or their demise.

Statistical analysis: The data were inputted into a Microsoft Excel spreadsheet. Categorical data were examined as proportions, while continuous data were analyzed in terms of means and standard deviations. Crude and bivariate logistic regression was employed to evaluate the factors linked to culture-positive analysis. Categorical data were examined using the Chi-square test, whereas mean and standard deviation were compared utilizing the independent Student's t-test. Variables exhibiting a P-value less than 0.05 were deemed significant determinants of early neonatal sepsis.

RESULT

A total of 268 participants were enrolled in the study, with 134 individuals diagnosed with neonatal sepsis (case) and 134 individuals without sepsis (control). All instances were classified as Early-Onset Neonatal Sepsis (EONS). 73.1% of the mothers of neonates were aged ≤35 years, while 44.8% of the mothers reported a history of fever during the third trimester of pregnancy (47.8% in the case group and 41.8% in the control group), 33.6% experienced urinary tract infections (56.7% in the case group and 10.4% in the control group), and 24.6% reported premature rupture of membranes (33.6% in the case group and 15.7% in the control group). 58.9% of the mothers were primigravidas (56.7% in the case group and 61.2% in the control group), and 50.7% had received antenatal care (42.5% in the case group and 58.9% in the control group). 63.8% of the neonates were delivered vaginally (63.4% in the case group and 64.2% in the control group), 87.3% were born at term gestation (85.8% in the case group and 88.8% in the control group), and 83.6% of the neonates exhibited normal birth weight (79.1% in the case group and 88.1% in the control group). [Table No.1]

Table No.1: Neonatal and maternal characteristic features of cases and control

Variables	Group	Case, n (%)	Control, n (%)
Maternal age (Year)	≤35 >35	98 (73.1%) 36 (26.9%)	123 (91.8%) 11(8.2%)
Gravida	Primi Multi	76 (56.7%) 58 (43.3%)	82 (61.2%) 52 (38.8%)
Mode of delivery	LSCS NVD	49 (36.6%) 85 (63.4%)	48 (35.8%) 86 (64.2%)
Fever		64 (47.8%)	56 (41.8%)
UTI		76 (56.7%)	14 (10.4%)
ANC		57 (42.5%)	79 (58.9%)
PROM		45 (33.6%)	21 (15.7%)
Gestation	Preterm Term	19 (14.2%) 115 (85.8%)	15 (11.2%) 119 (88.8%)
APGAR score	≤5 >5	61 (45.5%) 73 (54.5%)	47 (35.1%) 87 (64.9%)
Birth weight	<2.5 ≥2.5	28 (20.9%) 106 (79.1%)	16 (11.9%) 118 (88.1%)
Out come	Discharge Death	104 (77.6%) 30 (22.4%)	124 (92.5%) 10 7.5%)

The bivariate logistic regression module showed that maternal aged more than 35 years had a significant higher risk of Early Onset of sepsis (AOR 3.0242, 95% CI: 1.2421 to 6.8532, p=0.0151) compared to those born to mothers less than 35 years of age. Maternal UTI during pregnancy was a strong risk

factor for EOS (AOR 5.3833, 95% CI: 2.5972–11.2183, p<0.0001), and PROM was associated with an increased risk of EOS (AOR 2.8317, 95% CI: 1.98–4.73, p=0.003). Receiving antenatal care showed a protective effect against EOS (AOR 0.5426, 95% CI: 0.2543–1.0243, p=0.0458). Other factors, like mode of delivery (NVD verses LSCS), maternal fever, gravida status (primi verses multi), gestational age (preterm verses term), birth weight, and APGAR score at birth, did not show a statistically significant association with EOS (p-values >0.05). In summary, maternal UTI, maternal age ≥35 years, PROM, and lack of antenatal care were significant risk factors associated with EOS in this study. [Table No.2]

Outcome: Survival (discharge) rates were lower among cases (77.6%) compared to controls (92.5%). Mortality was significantly higher in cases (22.4%) than controls (7.5%). Outcomes (survival) were poorer in the case group compared to the control group.

Table No.2: Bivariate logistic regression for risk factors of EOS

Factors	Case	Control	Adjusted Odd ratio	95% CI	P value
Maternal age					
<35 Year	98	123	0.7356	0.3518 to 1.4806	0.4281
≥35 Year	36	11	3.0242	1.2421 to 6.8532	0.0151
UTI	76	14	5.3833	2.5972 to 11.2183	<0.0001
PROM	45	21	2.8317	1.98 to 4.73	0.003
Mode of delivery					
• NVD	85	86	1.0000	0.5314 to1.8124	1.0000
• LSCS	49	48			
Fever	64	56	1.2845	0.6482 to 2.5161	0.4218
Gravida					
• Primi	76	82	1.0841	0.4891 to 2.2043	0.7628
• Multi	58	52			
ANC	57	79	0.5426	0.2543 to 1.0243	0.0458
Gestation					
• Preterm	19	15	1.3654	0.4602 to 3.1242	0.6369
• Term	115	119	0.7531	0.3182 to 1.9893	0.6369
Birth weight					
<2.5 Kg	28	16	1.1214	0.4538 to 2.9012	0.8219
≥2.5 Kg	106	118			
APGAR score					
≤5	61	47	1.4315	0.7810 to 2.6953	0.2482
>5	73	87			

Escherichia coli was the most prevalent organism (54 cases, 40.3%). It was more common among term neonates (70.4%) and in babies weighing less than 2.5 kg (75.9%). Enterococcus accounted for 19.4% of cases, also seen more in term neonates (69.2%) and slightly more frequently in low birth weight babies (42.3%). Klebsiella pneumoniae was responsible for 15.7% of cases, predominantly in term babies (76.2%) and in those with a birth weight ≥2.5 kg (71.4%). Staphylococcus aureus appeared in 9.7% of cases, mainly in term neonates (76.9%) and those ≥2.5 kg (61.5%). Coagulase-Negative Staphylococcus (CONS) contributed to 8.9% of infections, with a strong predominance in term neonates (91.7%) and higher birth weight infants (83.3%). Methicillin-Resistant Staphylococcus aureus (MRSA), though less common (4.5%), was exclusively seen in term neonates (100%) and in that ≥2.5 kg (100%). Pseudomonas aeruginosa was the least common (2.2%), occurring only in term neonates and exclusively in that weight is normal.

[Table No.3] Most infections were more common in term neonates (>37 weeks) rather than preterm. A significant number of infections, especially with E. coli and CONS, were associated with low birth weight (<2.5 kg). MRSA and Pseudomonas infections were only noted in term, normal birth weight babies.

Table No.3: Microbiological Profile of EONS and its correlation with gestational age and birth weight

	Cases	Gestational age		Birth weight	
Organism	**Total n (%)**	**<37 weeks**	**>37 weeks**	**<2.5Kg**	**≥2.5Kg**
Escherichia coli	54 (40.3%)	16 (29.6%)	38 (70.4%)	13 (24.1%)	41 (75.9%)
Enterococcus	26 (19.4%)	8(30.8%)	18(69.2%)	11(42.3%)	15(57.7%)
Klebsiella pneumoniae	21(15.7%)	5(23.8%)	16(76.2%)	6(28.6%)	15(71.4%)

Staphylococcus aureus	13(9.7%)	3(23.1%)	10(76.9%)	5(38.5%)	8(61.5%)
Coagulase Negative Staphylococcus	12(8.9%)	1(8.3%)	11(91.7%)	2(16.7%)	10(83.3%)
Methicillin Resistant Staphylococcus aureus	6(4.5%)	0	6(100%)	0	6(100%)
Pseudomonas aeruginosa	3(2.2%)	0	3(100%)	0	3(100%)

Among gram-negative organisms, *E. coli* was highly resistant to ampicillin (88.9%) followed by cefoxitin (66.7%). Similarly Klebsiella was also highly resistant to ampicillin (80.9%) followed by cefoxitin (71.4%). *Pseudomonas* was highly resistant to piperacillin (100%) followed by imipenem and ciprofloxacin (66.7% each). Among gram-positive organism, *Enterococcus* was highly resistant to ampicillin (80.8%). Out of 25 isolates of *S.* aureus, 13 (52%) were Methicillin Resistant Staphylococcus aureus (MRSA). Out of 12 Methicillin Resistant Staphylococcus aureus (MSSA) isolates 8 (66.7%) were resistant to penicillin. [Table No.4].

Table No. 4: Antibiotic resistance pattern of causative organisms in early onset neonatal sepsis

Antibiotic	**Bacterial isolates**						
	E. coli n=54, (%)	*Enterococcus* n=26 (%)	*Klebsiella* n=21, (%)	*S. aureus* n=13, (%)	CoNS n=12, (%)	MRSA n=6, (%)	*Pseudomonas* n=3, (%)
Penicillin				13 (100%)	8(66.7 %)	6(100%)	
Ampicillin	48(88.9 %)	21(80.8%)	17 (80.9%)				
Piperacillin							3 (100%)
Cefoxitin	36(66.7 %)		15(71.4%)	00	00	6(100%)	
Ceftazidime	11(20.4 %)		8(38.1%)				1 (33.3%)
Cefepime	8(14.8 %)		4(19.5%)				1 (33.3%)
Imipenem	00		1(4.8%)		00		2 (66.7%)
Ciprofloxacin	00	6(23.1%)	1(4.8%)	00	00	4(66.7%)	2 (66.7%)
Gentamicin	1(1.8%)	00	2(9.5%)		2(16.7 %)		1(33.3%)
Tetracycline	00	00	1(4.8%)	00	00	2(33.3%)	

There is a high level of resistance to first-line antibiotics (Penicillin, Ampicillin) among most isolates. Resistance to higher-generation antibiotics like cephalosporins and even carbapenems is emerging, particularly in *Pseudomonas*. MRSA and *Pseudomonas* exhibit multi-drug resistance (MDR), posing a significant treatment challenge.

DISCUSSION

This research was designed to evaluate neonatal and maternal risk factors associated with the development of early-onset neonatal sepsis (EONS) in infants born at a tertiary center in a remote northern region, with the aim of facilitating preventive strategies and ensuring effective treatment of EONS. This research demonstrated that asymptomatic urinary tract infections (UTIs) during the third trimester, maternal age exceeding 35 years, and premature rupture of membranes (PROM) serve as significant predictors of early-onset neonatal sepsis (EONS). A comparable finding was observed in the meta-analysis encompassing studies from various regions globally, which indicated that laboratory-confirmed maternal infection and premature rupture of membranes (PROM) substantially elevated the risk of early-onset neonatal sepsis (EONS). [12, 18] In this research, neonatal factors including prematurity, low birth weight (LBW), and an APGAR score ≤5 at 5 minutes did not demonstrate a significant association with early-onset neonatal sepsis (EONS). Prematurity and LBW have been identified as significant risk factors for EONS in multiple earlier studies. [19,20] Nevertheless, certain earlier investigations reported a lack of association between EONS and preterm birth or low birth weight (LBW). [21, 22] In this research, gram-negative bacteria (Klebsiella pneumoniae and Pseudomonas aeruginosa) were frequently isolated from blood cultures in individuals suspected of having sepsis. Within gram-positive bacteria, coagulase-negative staphylococci (CONS) and Staphylococcus aureus were the organisms most frequently isolated. A prior investigation conducted in India identified Staphylococcus aureus and Klebsiella as the

predominant organisms associated with EONS. [23, 24]

CONCLUSION

Proper and sufficient antenatal screening for diagnosis and treatment of maternal infection as well as high-risk pregnancy screening for perinatal management of newborn to prevent neonatal sepsis related morbidity and death are stressed by this study. Usually isolated bacteria were MDR, which is a worrying indication of inappropriate and wrong antibiotic use and a major obstacle in clinical management. To create predictive models of sepsis risk, chance of infection at birth, and neonatal sepsis treatment protocol, more multicenter studies with big sample size are necessary.

Limitation of the study: Regarding limitations, the study was monocentric with a modest sample size, encompassing both cases and controls administered at the same institution. Secondly, the study lacked comprehensive socio-demographic data regarding the mother, which could be correlated with Early Onset Neonatal Sepsis (EONS). In conclusion, the detailed characterization of multidrug resistance (MDR) in organisms such as extended-spectrum beta-lactamases and methicillin-resistant Staphylococcus aureus (MRSA), as well as molecular-based specifications, could not be achieved due to the absence of a well-established facility.

REFERENCES

1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. (2005) 6(1):2–8. doi: 10.1097/01.PCC.0000149131.72248.E6
2. Mubiru A. The prevalence of neonatal sepsis and associated factors among neonates admitted to the neonatal intensive care unit of Jinja Regional Referral Hospital. 2018.
3. Bayana E, Endale K, Olani A, Birtatu Y, Tegenu K. Neonatal sepsis among neonates at public hospitals in Jimma, Ethiopia. Int J Pediatr. (2020) 8(9):12011–21. doi: 10.22038/ijp.2020.44435.3681
4. Rawat S, Neeraj K, Preeti K, Prashant M. A review on type, etiological factors, definition, clinical features, diagnosis management and prevention of neonatal sepsis. Journal of Scientific and Innovative Research. (2013) 2(4):802–13.
5. Schrag SJ, Cutland CL, Zell ER, Kuwanda L, Buchmann EJ, Velaphi SC, et al. Risk factors for neonatal sepsis and perinatal death among infants enrolled in the Prevention of Perinatal Sepsis Trial, Soweto, South Africa. Pediatr Infect Dis J. (2012) 31(8):821–6. doi: 10.1097/INF.0b013e31825c4b5a
6. Cizmeci MN, Kara S, Kanburoglu MK, Simavli S, Duvan CI, Tatli MM. Detection of cord blood hepcidin levels as a biomarker for early-onset neonatal sepsis. Med Hypotheses. (2014) 82(3):310–2. doi: 10.1016/j.mehy.2013.12.017
7. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr 2015;166:1070-4. doi: 10.1016/j.jpeds. 2014.12.023.
8. Tewari VV, Jain N. Monotherapy with amikacin or piperacillin-tazobactum empirically in neonates at risk for early-onset sepsis: A randomized controlled trial. J Trop Pediatr 2014;60:297-302. doi: 10.1093/tropej/fmu017.
9. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017;390:1770-80. doi: 10.1016/S0140-6736 (17) 31002-4.
10. Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. BJOG 2017;124:e280-305. doi: 10.1111/1471-0528.14821.
11. Bedford Russell AR, Kumar R. Early onset neonatal sepsis: Diagnostic dilemmas and practical management. Arch Dis Child Fetal Neonatal Ed 2015;100:F350-4. doi: 10.1136/ archdischild-2014-306193.
12. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: A global systematic review and meta-analysis. PLoS Med 2013;10:e1001502. doi: 10.1371/journal.pmed. 1001502.
13. Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics 2010;126:903-9. doi: 10.1542/peds.2010-0935.
14. World Health Organization. (2015). Integrated management of childhood illness: management of the sick young infant aged up to 2 months: IMCI chart booklet. World Health Organization. https://iris.who.int/handle/10665/326448. License: CC BY-NC-SA 3.0 IGO.
15. Rafi MA, Miah MMZ, Wadood MA, Hossain MG. Risk factors and etiology of neonatal sepsis after hospital delivery: A case-control study in a tertiary care hospital of Rajshahi, Bangladesh. PLoS One 2020;15:e0242275. doi: 10.1371/ journal.pone.0242275.
16. Edward L. Koneman's color atlas and textbook of diagnostic microbiology, 6th edition. Plastic and Reconstructive Surgery 2010;125:414-5. DOI: 10.1097/01. prs.0000358868.74684.60.
17. CLSI. Performance standard for antimicrobial susceptibility testing. 26th d CLSI supplements M100. 2015: Wayne PA: clinical and laboratory standards institute.
18. Masanja PP, Kibusi SM, Mkhoi ML. Predictors of early onset neonatal sepsis among neonates in Dodoma, Tanzania: A case control study. J Trop Pediatr 2016;66:257-66. doi: 10.1093/tropej/fmz062.
19. Quddus AR, Islam MN, Uddin MB, Mahmud AA, Badruzzaman M, Saha SK, *et al*. Study of risk factors, causative organisms and their sensitivity pattern in neonatal sepsis in a community based tertiary level hospital. Mymensingh Med J 2019;28:839-48.
20. Schrag SJ, Cutland CL, Zell ER, Kuwanda L, Buchmann EJ, Velaphi SC, *et al*. Risk factors for neonatal sepsis and perinatal death among infants enrolled in the prevention of perinatal sepsis trial, Soweto, South Africa. Pediatr Infect Dis J 2012;31:821-6. doi: 10.1097/INF.0b013e31825c4b5a.
21. Masanja PP, Kibusi SM, Mkhoi ML. Predictors of early onset neonatal sepsis among neonates in Dodoma, Tanzania: A case control study. J Trop Pediatr 2020;66:257-66. doi: 10.1093/tropej/fmz062.

22. Gebremedhin D, Berhe H, Gebrekirstos K. Risk factors for neonatal sepsis in public hospitals of Mekelle City, North Ethiopia, 2015: Unmatched case control study. PLoS One 2016;11:e0154798. doi: 10.1371/journal.pone.0154798.
23. Mohakud NK, Mishra JP, Nayak MK, Mishra J, Pradhan L, Panda SS, *et al*. Bacteriological profile and outcome of culture-positive neonatal sepsis in a special newborn care unit setting, Odisha. Cureus 2022;14:e25539. doi: 10.7759/ cureus.25539.
24. Marwah P, Chawla D, Chander J, Guglani V, Marwah A. Bacteriological profile of neonatal sepsis in a tertiary-care hospital of Northern India. Indian Pediatr 2015;52:158-9.