Neonatal Candidemia: Clinical Presentation, Laboratory Profile, Risk Factors and Immediate Outcome in a Tertiary Hospital in Kerala- A Case-Control Study

By Dr. Jayaram Sankar. KR, Dr. Sunil Daniel & Dr. Rekha Rachel Philip

Abstract- Objective: To identify the clinical and laboratory profile and risk factors of bloodstream candida infection in newborns and to assess the immediate outcome of candidemia in newborns.

Design: Case - control study.

Setting: Tertiary care NICU of Govt. T.D. Medical College, Alappuzha, Kerala from 1st January 2010 to 31st December 2014.

Methods: Through consecutive sampling, we got 94 cases and 188 controls. For comparison, chi-square test was used, and for strength association Odds ratio was used. Analysis was done using SPSS V18. Binary logistic regression has been used to identify independent risk factors.

Keywords: neonatal candidemia, silent hypoxemia, sub threshold feed tolerance.

GJMR-F Classification: NLMC Code: WS 205
Neonatal Candidemia: Clinical Presentation, Laboratory Profile, Risk Factors and Immediate Outcome in a Tertiary Hospital in Kerala- A Case-Control Study

Dr. Jayaram Sankar. KR °, Dr. Sunil Daniel σ & Dr. Rekha Rachel Philip ρ

Abstract- Objective: To identify the clinical and laboratory profile and risk factors of bloodstream candida infection in newborns and to assess the immediate outcome of candidemia in newborns.

Design: Case - control study.

Setting: Tertiary care NICU of Govt. T.D. Medical College, Alappuzha, Kerala from 1st January 2010 to 31st December 2014.

Methods: Through consecutive sampling, we got 94 cases and 188 controls. For comparison, chi-square test was used, and for strength association Odds ratio was used. Analysis was done using SPSS V18. Binary logistic regression has been used to identify independent risk factors.

Results: In our study the prevalence rate of neonatal candidemia was 3.89%. Silent hypoxemia (OR – 50.54, CI – 6.66, 383.41) and sub-threshold feed tolerance (OR – 3.38, CI – 2.81, 4.07) were found to be two symptoms of neonatal candidemia with high specificity. The mortality rate among neonates with candidemia was 18.1%, and in controls was 8.5% . The mean hospital stay of cases were 25.17 days, and of controls were 10.46 days.

Conclusion: Management of maternal vaginal candidiasis, judicious use of antibiotics, maintaining euglycemia, and early enteral feeding may reduce the risk for neonatal candidemia. Duration of hospital stay and mortality were high in neonates with candidemia. Silent hypoxemia and sub-threshold feed tolerance are two specific symptoms to suspect neonatal candidemia.

Keywords: neonatal candidemia, silent hypoxemia, sub threshold feed tolerance.

I. Introduction

Neonatal sepsis is frequently due to organisms colonizing the skin and mucosal surfaces, such as Coagulase-negative Staphylococci and Candida (1). Blood stream infection (BSI) due to Candida species in the neonatal intensive care unit (NICU) is less frequent than that due to Gram-positive or Gram-negative bacteria, but it has higher morbidity and mortality rates (2). Candida is the third most common etiologic agent in late-onset neonatal sepsis and is responsible for 8 to 15% of hospital-acquired infections (3). Preterm infants have high Candida colonization rates compared to term infants, and it is well established that colonization with Candida is inversely proportional to gestational age (4, 5). Colonization precedes invasive Candida infection, and the number of colonization sites and density of skin colonization with Candida correlate with candidemia (6-8). Even though Candida albicans is the most prevalent yeast pathogen, BSIs caused by Candida non-albicans, particularly Candida parapsilosis complex and Candida glabrata complex has been increased in recent years (9, 10). Newborns who survived from invasive candidiasis frequently have a long-term neurological impairment, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia (9). Candida infections are responsible for an 'attributable mortality' of 18–25%, significant morbidity, and healthcare costs (11). The incidence and associated mortality due to candidemia can be influenced by several factors, including the population at risk, healthcare facility standards, Candida spp. involved and anti-fungal resistance (12).

Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis of candidemia is difficult. (13). Here, in this study, we are trying to identify the clinical and laboratory profile of neonatal candidemia and the risk factors associated with it.

Ethical consideration: Permission to conduct this study was obtained from the institutional research committee and ethical committee of Government T. D Medical College, Alappuzha.

II. Methods

This study was a retrospective case-control study. Sex matched cases and controls were selected through consecutive sampling by file review of newborns of NICU of Govt. T.D. Medical College from 1st January 2010 to 31ST December 2014. Cases were identified through the review of a meticulously maintained NICU logbook in which relevant details
(including the IP number, name, age, sex, date of admission, discharge diagnosis, date of discharge/death, and status at discharge) of all admitted cases were entered. We also reviewed the blood culture record of all cases and controls for final case confirmation from Microbiology Laboratory. All babies in whom blood culture yielded candida were considered as cases. Two newborns of the same-sex as that of the case and admitted within one week prior or after the case but negative for candida blood culture were considered for controls. Newborn babies who were on antibiotics before sampling for blood culture and whose case books incomplete or not available were excluded.

Case records of all these newborns were retrieved from the medical record library. After applying exclusion criteria, cases and controls were finalized. Details of risk factors (maternal, neonatal, and nosocomial), clinical features, investigation results, and outcome of all cases and controls were recorded in the proforma and analyzed.

III. Definitions

Candidemia: The blood culture yields candida species organisms.

Silent hypoxemia: Low Spo2 with no tachypnea/bradypnea/apnoea/respiratory distress/ hypothermia and with no evidence of shock.

Feed intolerance: The enteral milk feeding has to be stopped due to presence of one or more of the following- gastric residuals >50% of previous feed, vomiting, abdominal distension, visible bowel loops, and blood in the stool (occult/gross).

Sub-threshold feed tolerance: The gastric residue is 20-50% of previous feed consecutively for at least three times without features of feed intolerance.

For statistical analysis, continuous variables were summarized using mean and standard deviation and categorical variables using frequencies and percentages. To identify risk factors of candida infection, Chi-square test was used, and for the strength of association odds ratio was used. Binary logistic regression was performed using the enter method to identify independent predictors of neonatal candidemia and mortality associated with candidemia. All analysis was performed using SPSS V18.

IV. Results

From 1st January 2000 to 31st December 2014, there were 2754 admissions to the newborn nursery. Out of this, 107 (3.9%) had candidemia. Seven babies who were started on fluconazole before blood culture and 6 with incomplete case records were excluded from the study. Finally, 94 cases and 188 controls were included in this study. 92 (97.9%) cases were Candida nonalbicans, and the rest were candida albicans. Cases and controls were comparable concerning sex, route of delivery, and gravidity. The frequency of Gestational diabetes mellitus, Gestational hypertension, PROM, and 3rd trimester UTI was also comparable (Table 1).

| VARIABLE                  | CASE-94 (100%) | CONTROL-188 (100%) | P value |
|--------------------------|----------------|--------------------|---------|
| Sex (M)                  | 57(60.6)       | 114(60.6)          | .518    |
| Route of delivery (vaginal) | 42(44.7)     | 100(53.2)          | .207    |
| PrimiGravida             | 51(54.3)       | 114(60.6)          | .309    |
| GDM                      | 3(3.2)         | 6(3.2)             | 1.000   |
| GHT                      | 14(14.9)       | 19(10.1)           | .244    |
| PROM                     | 20(21.3)       | 23(12.2)           | .054    |
| 3rd trimester UTI        | 4(4.3)         | 7(3.7)             | 1.000   |

There was a significant difference in the mean age of admission between cases and controls. Symptoms & signs such as lethargy (67%), respiratory distress (67%), apnoea (35.1%), silent hypoxia (21.3%), seizure(14.9%), feed intolerance (33%), sub-threshold feed tolerance(16%), weak cry (86.2%), prolonged CFT (48.9%), mucosal candida infection (5.3%), abdominal distension (54.3%) and hepato-splenomegaly (22.3%) was significantly higher in cases (table-2). Newborn babies with candida BSI showed a significantly higher proportion of thrombocytopenia (75.5%), positive C-reactive protein (47.9%), and abnormal CSF (9.6%). Urine fungal hyphae (14.9%) were isolated only from neonates with candidemia. The mean WBC count was significantly lower in cases (10858) compared to controls (14191) (table-2).

| VARIABLE              | CASE-94 (100%) | CONTROL-188 (100%) | P value | OR   | 95% CI      |
|-----------------------|----------------|--------------------|---------|------|-------------|
| Age on admission (Mean & SD) | 1.10 (0.39)    | 1.74 (1.19)        | <0.001  | 8.29 | 4.74, 14.52 |
| Lethargy              | 63(67)         | 37(19.7)           | <0.001  | 8.29 | 4.74, 14.52 |
| Resp distress          | 63(67)         | 75(39.9)           | <0.001  | 8.29 | 4.74, 14.52 |
When the maternal risk factors associated with the development of candidiasis were analyzed, statistical significance was seen for maternal vaginal candidiasis at the time of labor and for mothers who had received antenatal steroids. Among the neonatal risk factors, prematurity, LBW, birth asphyxia, resuscitation which need bag and mask/ ET, delayed enteral feed >24 hours, and neonatal hyperglycemia was significantly associated with neonatal candidemia. Nosocomial risk factors significantly associated with neonatal candidemia were amino acid infusion, steroids, more than two antibiotics, central venous access, endotracheal intubation, assisted ventilation, oxygen, intravenous immunoglobulin, aminophylline, caffeine and surfactant. (Table-3)

Table-3: Comparison of risk factors associated with systemic candidiasis among cases and controls

| VARIABLES | CASES=94 | CONTROLS= 188 | P value | OR | 95% CI |
|-----------|----------|---------------|---------|----|--------|
| Preterm   | 80(81.5) | 77(41)        | <0.001  | 8.24 | 4.4, 15.6 |
| LBW       | 84(89.4) | 85(45.2)      | <0.001  | 10.2 | 4.98, 20.8 |
| Very preterm (<28wks) | 34 (36.2) | 19 (10.1) | <.001 | 5.04 | 2.7, 9.5 |
| Extremely LBW (<1.0kg) | 12 (12.8) | 5 (2.7) | 0.001 | 5.4 | 1.8, 15.7 |
| Ante natal steroid | 33(35.1) | 17(9.0) | <0.001 | 5.44 | 2.83, 10.47 |
| Maternal vaginal candidiasis | 18(19.1) | 5(2.75) | <0.001 | 8.668 | 3.106, 24.2 |
| Birth asphyxia | 31 (33) | 31 (16.5) | 0.002 | 2.49 | 1.4, 4.44 |
| Active Resuscitation | 24(25.5) | 23 (12.2) | 0.006 | 2.5 | 1.3, 4.6 |
| Delayed enteral feed (>24hrs) | 73(77.7) | 57 (30.3) | <0.001 | 7.99 | 4.49, 14.22 |
| Neonatal Hyperglycemia before C&S | 69(73.4) | 30 (16) | <0.001 | 14.5 | 8.26, 25.6 |
| Amino acid infusion | 78(83) | 32 (17) | <0.001 | 23.77 | 12.3, 45.93 |
| Steroid for baby | 12 (12.8) | 5 (2.7) | 0.002 | 5.36 | 1.83, 15.7 |
| Ranitidine | 7 (7.4) | 6 (3.2) | 0.134 | 2.44 | .796, 7.48 |
| More than 2 antibiotics used | 78(83) | 113 (60.1) | <0.001 | 3.24 | 1.8, 5.97 |
| CV catheter | 13 (13.8) | 3 (1.6) | <0.001 | 9 | 2.75, 35.7 |
| Endo-tracheal intubation | 33(35.1) | 16 (8.5) | <0.001 | 5.61 | 2.99, 11.3 |
| Assisted ventilation | 38(40.4) | 26 (13.8) | <0.001 | 4.23 | 2.36, 7.58 |
| Oxygen | 74(78.7) | 69 (36.7) | <0.001 | 6.4 | 3.6, 11.4 |
| Abdominal surgery | 3(3.2) | 3 (1.6) | 0.404 | 2.03 | 0.4, 10.3 |
| IVIG | 11 (11.7) | 6 (3.2) | 0.007 | 4.02 | 1.44, 11.24 |
| Aminophylline | 6 (6.4) | 0 (0) | <0.001 | 2.32 | 1.3, 3.73 |
| Caffeine | 54 (57.4) | 20 (10.6) | <0.001 | 11.34 | 6.1, 21.0 |
| Surfactant | 30 (31.9) | 15 (8.0) | <0.001 | 5.41 | 2.7, 10.7 |

As many of these risk factors are interdependent, inorder to identify the independent risk factors of candidemia, we did binary logistic regression. The independent risk factors were; more than two antibiotics, amino acid infusion, neonatal hyperglycemia before blood culture, and maternal vaginal candidiasis (table-4).
Table-4: Independent risk factors of neonatal candidiasis

| Variable                  | Adjusted odds ratio (95% CI) | P value |
|---------------------------|-----------------------------|---------|
| Maternal candidiasis      | 12.7 (2.5, 65.5)             | .002    |
| Amino acid infusion       | 5.5 (1.6, 18.7)              | .006    |
| More than 2 antibiotics   | 5.05 (1.8, 13.9)             | .002    |
| Hyperglycemia             | 10.9 (4.2, 28.1)             | <.001   |

The mortality rate among admitted newborns with candidemia and without candidemia was 18.1% and 8.5%, respectively. This finding was statistically significant. The mean duration of hospital stay among cases was also significantly higher. (table-5)

Table-5: Comparison of immediate outcome between cases and controls

| VARIABLE                  | CASE-94 (100%) | CONTROL-188 (100%) | P value | OR   | 95% CI |
|---------------------------|---------------|--------------------|---------|------|--------|
| Death                     | 17(18.1)      | 16(8.5)            | .018    | 2.37 | 1.14, 4.94 |
| Duration (days) of hospital stay (mean & SD) | 25.17(12) | 10.46(11.6) | <0.001 |       |        |

On univariate analysis, we found that the following were predictors for mortality in neonatal candidiasis; vaginal delivery, preterm <32 weeks GA, birth weight <1.5 kg, lethargy, respiratory distress, apnoea, prolonged CFT, skin mottling, endo tracheal intubation, assisted ventilation, administration of caffeine or surfactant, and abdominal surgery. (Table-6)

Table-6: Risk factors of mortality in neonatal candidemia

| VARIABLES                  | Death=17(100%) | Discharged=77(100%) | P value | OR   | 95% CI |
|---------------------------|----------------|---------------------|---------|------|--------|
| Route of delivery-vaginal | 13(76.5)       | 29(37.7)            | .004    | 5.38 | 1.6, 18.1 |
| <32 weeks gestation       | 12(70.6)       | 22(28.6)            | .001    | 6.0  | 1.9, 19.0 |
| ELBW & VLBW               | 14 (82.4)      | 31 (40.3)           | .002    | 6.9  | 1.8, 26.1 |
| Lethargy                  | 15(88.2)       | 48(62.3)            | .040    | 4.5  | 0.97, 21.3 |
| Respiratory distress      | 15(88.2)       | 48(62.3)            | .040    | 4.5  | 0.97, 21.3 |
| Apnoea                    | 13 (76.5)      | 20 (26)             | <0.001  | 9.3  | 2.7, 31.7 |
| Prolonged CFT             | 13 (76.5)      | 33 (42.9)           | 0.012   | 4.33 | 1.3, 14.5 |
| Skin mottling             | 6 (35.3)       | 5 (6.5)             | .001    | 7.86 | 2.0, 30.2 |
| Endotracheal Intubation    | 14 (82.4)      | 19 (24.7)           | <0.001  | 14.2 | 3.7, 55  |
| Assisted ventilation/CPAP | 16 (94.1)      | 22(28.6)            | <0.001  | 40   | 5, 320  |
| Abdominal surgery          | 2 (11.8)       | 1 (1.3)             | .026    | 10.1 | .86, 119 |
| Caffeine                   | 14 (82.4)      | 40 (51.9)           | .022    | 4.3  | 1.1, 16.2 |
| Surfactant                 | 10 (58.8)      | 20 (26)             | .009    | 4.1  | 1.37, 12.1 |
| Active resuscitation       | 8 (47.1)       | 16 (20.8)           | .025    | 3.39 | 1.12, 10.1 |

Multivariate regression analysis found out only three independent predictors of mortality. These were apnoea, abdominal surgery, and active resuscitation. (Table-7)

Table-7: independent risk factors for mortality in neonatal candidemia

| Variable                  | Adjusted odds ratio (95% CI) | P value |
|---------------------------|-----------------------------|---------|
| Apnoea                    | 36.3 (1.81, 74)             | .020    |
| Abdominal surgery         | 332 (1.3, 831)              | .039    |
| Active Resuscitation      | 14 (1.1, 186)               | .041    |
V. Discussion

We report a prevalence of 3.89% for neonatal candidemia during the study period. This prevalence rate is comparable to the prevalence reported from developed countries.\(^{14-16}\)

Our study found a significant difference in the age of admission between cases and controls contrary to a study from China\(^ {17}\).\(^ {17}\) This may be due to the difference in indications for admission among the hospitals.

The clinical features associated with neonatal candidemia reported in our study namely lethargy, respiratory distress, apnoea, silent hypoxia, seizure, feed intolerance, sub-threshold feed tolerance, weak cry, prolonged CFT, mucosal candida infection, abdominal distension, and hepatosplenomegaly were similar to that reported in the literature\(^ {18,19}\).\(^ {18,19}\) The two new signs we identified were silent hypoxemia (specificity- 99.46% and sensitivity-21%) and sub-threshold feed tolerance (specificity- 100% and sensitivity-15.9%), which is not reported in other studies. In some of the cases, these early signs were the reason for suspecting candidiasis.

We found that neonatal candidemia was significantly associated with thrombocytopenia, positive CRP, a relatively low total WBC count, and abnormal CSF, which is consistent with reports elsewhere.

Most of the significant risk factors for neonatal candidemia we obtained were documented in the literature\(^ {18,19,22,23}\).\(^ {18,19,22,23}\) Many of these factors are interdependent. Regression analysis revealed only four independent risk factors that are significantly associated with neonatal candidemia. Though the administration of ranitidine and abdominal surgery are reported to be significant risk factors, we could not find this association.

The death rate of neonates with candidemia was significantly higher than neonates without candidemia (18.1% vs. 8.5%). Other studies also report a higher death rate among systemic candidiasis compared to other inpatients of the NICU\(^ {24}\).\(^ {24}\) The duration of hospitalization was also high for cases.

The independent risk factors of mortality in neonatal candidemia were apnoea, abdominal surgery, and invasive resuscitation. The increased mortality in the babies who underwent abdominal surgery may be linked to large inoculum size of candida organisms, which is already colonized in GIT and use of broad-spectrum antibiotics after surgery, which may facilitate its growth. The anaerobic environment during apnoea and before resuscitation may facilitate adhesion, tissue invasion, and disruption of host immune function by candida through increased production of secretory aspartyl proteinases (SAP), which may increase the severity of the infection.

Our study has few limitations. We could not perform species differentiation among the candida organisms and antifungal susceptibility. Assessments of complications using USG abdomen & CT of the head could not be performed in many cases because of logistic problems.

In conclusion, in developing countries, Candidemia is a common cause of BSI among neonates. Candida nonalbicans is the predominant type identified. Two new signs (silent hypoxemia and sub-threshold feed tolerance) identified were more specific for neonatal candidemia. Management of maternal vaginal candidiasis during pregnancy, judicious use of antibiotics in newborns, maintaining euglycemia in the newborn period, early enteral feed, and avoiding amino acid infusion may help in the reduction of neonatal candidiasis. Early identification of this problem, especially among babies who had apnoea, active resuscitation, and abdominal surgery and managing them, may help to reduce mortality.

What is already known: Clinical diagnosis of neonatal candidemia is difficult
What this study adds: Silent hypoxemia and sub-threshold feed tolerance are two most specific features of neonatal candidiasis.

Acknowledgement: Dept. of microbiology, Govt. T.D. MCH, Alappuzha
Contributors: JSKR was the Principal investigator, SD participated in data collection and draft preparation, RRP helped in statistical analysis.

Funding: None

Competing interest: None stated

References Références Referencias
1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002; 110:285–291. [PubMed]
2. Giuseppina Caggiano,1 Grazia Lovero,1 Osvalda De Giglioet al “Candidemia in the Neonatal Intensive Care Unit: A Retrospective, Observational Survey and Analysis of Literature Data” BioMed Research International, Volume 2017, Article ID 7901763, 12 pages
3. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004; 39:309–317. [PubMed]
4. Ali GY, Alghory EH, Rashed KA, Almoghanum M, Khalifa AA. Prevalence of Candida colonization in preterm newborns and VLBW in neonatal intensive care unit: role of maternal colonization as a risk factor.
factor in transmission of disease. J Matern Fetal Neonatal Med. 2012; 25:789–795. [PubMed]
5. Bliss JM, Basavegowda KP, Watson WJ, Sheikh AU, Ryan RM. Vertical and horizontal transmission of Candida albicans in very low birth weight infants using DNA fingerprinting techniques. Pediatr Infect Dis J. 2008; 27:231–235. [PubMed]
6. Mahieu LM, Van Gasse N, Wildemeersch D, Jansens H, Ieven M. Number of sites of perinatal Candida colonization and neutropenia are associated with nosocomial candidemia in the neonatal intensive care unit patient. Pediatr Crit Care Med. 2010; 11:240–245. [PubMed]
7. Manzoni P, Farina D, Galletto P, et al. Type and number of sites colonized by fungi and risk of progression to invasive fungal infection in preterm neonates in neonatal intensive care unit. J Perinat Med. 2007; 35:220–226. [PubMed]
8. Bendel CM. Colonization and epithelial adhesion in the pathogenesis of neonatal candidiasis. Semin Perinatol. 2003; 27:357–364. [PubMed]
9. M. S. Kelly, D. K. Benjamin, and P. B. Smith, “The epidemiology and diagnosis of invasive candidiasis among premature infants,” Clinics in perinatology, vol. 42, no. 1, pp. 17–105, 2015; View at Publisher · View at Google Scholar · View at Scopus
10. E. Leibovitz, “Strategies for the prevention of neonatal candidiasis,” Pediatrics and Neonatology, vol. 53, no. 2, pp. 83–89, 2012. View at Publisher · View at Google Scholar · View at Scopus
11. Neu N, Malik M, Lunding A, et al. Epidemiology of candidemia at a Children’s hospital, 2002 to 2006. Pediatr Infect Dis J. 2009; 28:806–809. [PubMed], 30, 53.
12. Goel N, Ranian PK, Aararwal R, Chaudhavr U, Sanieev N. Emergence of non albicans Candida in neonatal septicemia and antifungal susceptibility: Experience from a reference tertiary care center. J Lab Physicians. 2009; 1(2):53-5.
13. Ariff S, Saleem AF, Soofi SB, Sajjad R. Clinical spectrum and outcomes of neonatal candidiasis in a tertiary care hospital in Karachi, Pakistan. J Infect DevCtries. 2011; 5:216-23.
14. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, Blumberg HM, Patterson JE, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W (2000). Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. Pediatr Infect Dis J 19: 319-324.
15. Howell A, Isaacs D, Halliday R. Australasian Study Group for Neonatal Infections. Oral nystatin prophylaxis and neonatal fungal infections. Arch Dis Child Fetal Neonatal Ed. 2009; 94(6): 429–433.[PubMed]
16. Segal E (2004) Candida still number one – what do we know and where are we going from here? Mycoses 48: 1.3-11. PMID:15887329
17. Jichang Chen, Yongjiang Jiang, Ba Wei, Yanling Ding, Shaolin Xu, Peixu Qin, and Jinjian Fu. Epidemiology of and risk factors for neonatal candidemia at a tertiary care hospital in western China.BMC Infect Dis. 2016; 16: 700.
18. John P. Cloherty, Eric C. Eichenwald, Annie R. Hansen, Ann r. Stark. Manual of Neonatal Care. 7th ed; south Asian ed, Wolters Kluwer Pvt Ltd New Delhi.
19. Christine A. Gleason, Sherin U. Devaskar. Avery’s Diseases of Newborn. 9th ed Elsevier, India; 2012
20. Dr. ArchanSil, Dr. Amit Das, Dr. Mithun Chandra Konar. A study on clinico-Mycoligical profile of systemic fungal infection in Neonates: an Indian Perspective. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 16, Issue 5 Ver. VII (May. 2017), PP 117-120 www.iosrjournals.org
21. Marisol Fernandez, Edina H. Moylett, Daniel E. Noyola, Carol J. Baker: Candidal Meningitis in Neonates: A 10-Year Review. Clinical Infectious Diseases. Volume 31, Issue 2, 1 August 2000; Pages 458–463;https://doi.org/10.1086/313973.
22. B. D. W. Chow, J. R. Reardon, E. O. Perry, S. S. Laforce-Nesbitt, R. Tucker, and J. M. Bliss; Expressed Breast Milk as a Predictor of Neonatal Yeast Colonization in an Intensive Care Setting. J Pediatric Infect Dis Soc. 2014 Sep; 3(3): 213–220
23. Benjamin DK, Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117:84–92
24. Heather Cahan and Jaime G. Deville. Outcomes of Neonatal Candidiasis: The Impact of Delayed Initiation of Antifungal Therapy. Int J Pediatr. Volume 2011; Article ID 813871, 6 pages, http://dx.doi.org/10.1155/2011/813871