http:// ijp.mums.ac.ir
Original Article (Pages: 9719-9728)

Fungal Colonization among Iranian Infants Hospitalized in the Neonatal Intensive Care Unit: Occurrence Rate, Risk Factors and Health Outcome

Mehrdad Rezaei[1], *Mozhgan Moghtaderi[1], *Parisa Badiee[2], Zahra Zahadatpoor[1], Gholamreza Pooladfar[2]

[1]Neonatal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Background: Fungal infections with high morbidity and mortality in neonatal intensive care unit are usually preceded by colonization. We aimed to investigate the prevalence of fungal colonization, determine the risk factors and health outcome such as any change in the patient's improvement in hospitalized infants of Neonatal Intensive Care Unit (NICU).

Materials and Methods: This prospective cohort study was conducted on all newborns who were hospitalized in Namazee NICU which is the largest neonatal center in Southwestern Iran during the six- month period from January to July 2018. The eye, urine, perineum, nose, throat, umbilicus and blood were sampled within 72 hours following NICU admission and repeated one week later. Each newborn with at least one positive fungi culture from surveillance site was defined as fungal colonization. All newborns were categorized into two groups based on results of fungal colonization; they were evaluated for baseline perinatal and neonatal characteristic data, probable risk factors (such as prior antibiotics, presence of an endotracheal tube and neonatal disease) and health outcomes (cure, improvement or death). Statistical analysis was done using SPSS software (version 22.0).

Results: From a total of 105 (37 girls, 68 boys) hospitalized newborns in NICU, forty-eight (45.7%) of them were colonized by Candida spp. which was the only fungus isolated from the cultures. There were significant differences for the level of hemoglobin (p= 0.04) and cardiac diseases (p= 0.04) between the two groups of fungal colonization and non -colonized newborns. One-third of the newborns that had fungal colonization passed away vs. one-tenth without fungal colonization.

Conclusion

Based on the results, there was a 45.7% rate of fungal colonization in hospitalized newborns in NICU. Hemoglobin level and cardiac diseases were a risk factor for fungal colonization in these patients. The rate of death was approximately three-fold in hospitalized infants with fungal colonization vs. non fungi infected.

Key Words: Colonization, Fungi, Newborn, Neonatal Intensive Care Unit.

*Please cite this article as: Rezaei M, Moghtaderi M, Badiee P, Zahadatpoor Z, Pooladfar Gh. Fungal Colonization among Iranian Infants Hospitalized in the Neonatal Intensive Care Unit: Occurrence Rate, Risk Factors and Health Outcome. Int J Pediatr 2019; 7(7): 9719-28. DOI: **10.22038/ijp.2019.39554.3371**

Corresponding Authors:

Mozhgan Moghtaderi (M.D), Neonatal Research Center, Shiraz University of Medical Sciences, Zand St., 71 36122218, Shiraz, Iran, AND Parisa Badiei (M.D), Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Zand St., +98 7193711351, Shiraz, Iran.

Email: moghtadery@sums.ac.ir AND badieep@sums.ac.ir

Received date: Jan.17, 2019; Accepted date: Apr. 22, 2019

1- INTRODUCTION

Fungi are a common cause of infections in critically ill infants and play an important role in infectious-related mortality of neonatal intensive care unit (NICU). Neonatal fungal infection is firstly preceded by transmission of fungi through the passage of birth canal or the hands of health care professionals. This vertical or horizontal transmission is usually the reason of fungal colonization and subsequent infection in newborns (1-3). The most prevalent groups of colonizing fungi are Candida species (C. spp.), and adherence of C. spp. to the skin, mucosa and catheter surface leads to colonization (4, 5). Besides properties of the fungi, fungal colonization has been associated with a wide range of risk factors. Newborns' factors including immature lymphocyte and antibody systems, moist skin surface, and atopic dermatitis, and sometimes necrotizing enterocolitis (NEC) predisposes them to fungal infections. Newborns with central vascular catheter and endotracheal tube may be vulnerable to fungal infections.

Different studies have demonstrated relationships between usages of medications such as antibiotics, histamine 2 antagonists and post-natal steroids with fungal colonization in NICU hospitalized newborn. Intravenous infusates such as parental nutrition and lipid emulsions may transmit the fungi directly to blood circulation (5-11). Most fungal colonization occurs by 2 weeks of life in newborns. Among candida spp., candida albicans is the most prevalent species that is present in 50 to 97% of very low birth newborns. Candida is the second most frequent species associated with the presence of a central venous catheter, using histamine 2 antagonists and cephalosporin in newborns. Candida glabrata affects the low birth newborns with NEC. Other candida species reported to cause sepsis in low birth weight (LBW) infants include candida tropicalis, candida krusei, candida lusitaniae, candida guilliermondii, and candida. Dubliniensis (1, 12, 13). Despite improvements in the survival rates of high risk infants, fungal colonization remains an important contributing factor to neonatal morbidity and mortality. The aims of this study were to investigate the prevalence of fungal colonization, determine the risk factors and health outcome in the infected infants in NICU in Southwestern Iran.

2- MATERIALS AND METHODS

2-1. Method

This prospective cohort study was conducted in Namazee NICU, which is the largest neonatal care center in Fars province, Southwestern Iran. All newborns who were hospitalized in NICU during the six- month period from January to July 2018 were included in this study. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1395.S411).

The design and objectives of the study were explained to the neonates' parents, and written informed consent was obtained from the parents who were willing to participate in the study. A trained nurse filled out a researcher made questionnaire, recorded the information for laboratory data and obtained results of fungal cultures from surveillance site in all newborns. Then, the newborns were categorized into two groups based on positive or negative fungal colonization, they were evaluated for baseline characteristic data, probable risk factors and health outcomes.

2-2. Researcher made Questionnaire

The researcher made questionnaire was categorized into three parts and filled out via face-to-face interviews with the newborns' parents and reading the newborns' medical chart in the hospital. Three parts of the questionnaire were

baseline characteristics, probable fungal risk factors and health outcome. The first part included five questions about birth date, gestational age, sex, age of admission, and birth weight; the second part included information for fifteen items consisting of mode of delivery (cesarean section or vaginal delivery), NEC, cardiac disease, premature rupture of membrane (PROM) more than 18 h in the mother, dwelling central venous catheter, endotracheal intubation, rescue history, hospitalization duration, chest tube, blood transfusion, type of antibiotic therapy, phototherapy, use of antibiotics (vancomycin, carbapenems, third-generation of cephalosporin), use of ranitidine and multiple antibiotic (≥3 types of antibiotics); the third part was used to obtain information for three newborns' outcome including cure, improvement with transfer to the ward or death.

2-3. Laboratory tests and fungal colonization

Laboratory tests including complete blood count (CBC) and C-reactive protein (CRP) were measured at the time of the newborns' admission. The eye, urine, perineum, nose, throat, umbilicus and blood were sampled within72 h following NICU admission and repeated one week later. Sampling techniques were standardized across the sites. In brief, standard sterile red-top culture swabs were used to sample the eye, nose, throat, perineum (just anterior to the anus) and umbilicus as well as using catheter for urine specimen. The fungi were isolated from the blood cultures, using the Bactec. All the samples were transported to Professor Alborzi Clinical Microbiology Research Center, placed on Sabouraud dextrose agar (Merck, Darmstadt, Germany), and incubated at room temperature (24 ℃) for 7 days. The purity of the isolated species was evaluated by culturing on potato dextrose agar (OXOID LTD, Basingstoke, Hampshire, England). The identification of candida strains was performed using germ tube and by PCR-RFLP analysis using ITS region, ITS1 5′ -TCC GTA GGT GAA CCT GCG G-3′ and ITS4 5 ′ -TCC TCC GCT TAT TGA TAT GC-3 ′ and the restricted enzyme MspI (Thermo Scientific, USA) (15). Candida parapsilosis ATCC 22019 were used as controls. Each newborn had had repeat sampling from 7 sites; the fungal colonization was defined based on the isolation of a fungal species from at least one surveillance site.

2- 4. Inclusion and exclusion criteria

Eligible study participants included hospitalized neonates in NICU, born between January and July 2018, alive till 14 days old, whose parents gave required information for the study. The cases with incomplete fungal sampling and lacking exact information were excluded.

2-5. Statistical analysis

Chi-square, independent sample t-test and Mann-Whitney test were used to determine the frequency, mean and compare the mean of fungal colonization with risk factors. Analyses were conducted using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was set at $p<0.05$.

3- RESULTS

A total of 105 (37 girls, 68 boys) newborns hospitalized in NICU with an age range of 1 day to 90 days (mean 12.58± 13.44 days) were studied. The mean of newborns' birth weight was 2516± 823 g, twenty-one (20%) were ≤ 1500 g, and 84 (80%) were more than 1500 gr. The median duration of NICU admission was 16.46± 10.77 days. Forty-eight out of 105 newborns (45.7%) were colonized by candida spp. which was the only fungus isolated from the cultures. **Table.1** represented the baseline data and laboratory results in patients with fungal

colonization as compared to their non-colonized newborns; the level of hemoglobin between the two groups was significantly different. There was no association between birth weight ≤ 1000 g and gestational age < 32 weeks with fungal colonization (p= 0.8 and p= 0.06, respectively). The frequency of probable risk factors in newborns with and without fungal colonization is shown in **Table.2**. Fungal colonization had a significant positive correlation with newborn's cardiac disease (p= 0.04, r= 0.2), while it showed a negative correlation with endotracheal intubation (p= 0.03, r= -0.2) (Table.2). The type of cardiac diseases among 52 newborns that had identified abnormality in echocardiography includes: patent ductus arteriosus (PDA) in 38 (73%), ventricular and septal defect each in 18(34.6%), coarctation of the aorta in 3(5.8%), Tetralogy of Fallot in 2(3.8%), transposition of the great arteries and double outlet right ventricle each in 1(1.9%) newborn. All hospitalized newborns were treated with multiple antibiotics (≥3 types of antibiotics); therefore, we cannot compare this factor between our two studied groups. Among 1,570 surveillance specimens for fungal culture in all hospitalized newborns, 140 were positive for candida spp. The most frequency observed was candida albicans 76(54.3%), followed by candida parapsilosis 34(24.3%), candida famata 11 (7.9%), candida glabrata10 (7.1%), and candida kefyr9 (6.4%). Early colonization within 72 h following admission occurred in 134 (95.7%) newborns and one week later in 6 (4.3%). Out of 140 samples for fungal colonization, the risk of infection was highest for perineum colonization (n=56, 40%), followed by throat (n=30, 21.4%), urine (n=25, 17.9%), nose (n=14, 10%), eye (n=8, 5.7%), and umbilicus (n=6, 4.3%); however, one newborn (0.7%) showed growing of fungi in the blood. Out of 48 newborns with fungal colonization, multiple-site fungal colonization (two or more sites) was detected in 29 infants (60.4%). One-third of the newborns with fungal colonization passed away vs. one- tenth without fungal colonization. As shown in **Table.3**, health outcome had a significant correlation with fungal colonization in the NICU hospitalized newborns (p= 0.02).

Table-1: Demographic data and baseline laboratory results in the study groups with and without fungal colonization (n=105)

Characteristics	Mean ± SD		P- value
	Cases with fungal colonization, n=48 Mean ± SD	Cases without fungal colonization, n=57 Mean ± SD	
Gestational age (week)	35.35± 4.43	35.75± 3.60	0.61
Age (days)	14.37± 16.65	11.07± 9.88	0.09
Birth weight (g)	2508.75±844.24	2522.2±812.81	0.93
Gender, n (%) Female Male	 20(41.6%) 28(58.4%)	 17(29.8%) 40(70.2%)	0.20
Duration of admission (days)	17.43± 10.52	15.64± 11.01	0.40
White blood cell(cell/mm3)	10738± 4760	10470± 5055	0.72
Platelet(cell/mm3)	218857±150923	22322±124396	0.81
Hemoglobin(g/dL)	11.26± 2.96	12.27± 2.23	0.04*
C-reactive protein	10.47± 15.50	7.03± 6.57	0.13

* Significant correlation; SD: Standard deviation.

Table-2: The frequency of probable risk factors in NICU newborns with and without fungal colonization (n=105)

Variables	Number		P- value
	Cases with fungal colonization, n=48 Number (%)	Cases without fungal colonization, n=57 Number (%)	
Type of delivery Cesarean section Vaginal delivery	33(68.7) 15(31.3)	45(78.9) 12(21.1)	0.23
Necrotizing enterocolitis Yes No	1(2) 47(47)	5(8.8) 52(91.2)	0.14
Cardiac disease Yes No	29(60.4) 19(39.6)	23(40.4) 34(59.6)	0.04*
Premature rupture of membrane Yes no	1(2) 47(47)	3(5.3) 54(94.7)	0.33
Endotracheal intubation Yes No	1(2) 47(47)	8(14) 49(86)	0.02*
Resuscitation history Yes No	28(58.3) 30(41.7)	20(35) 37(65)	0.39
Chest tube Yes No	4(8.3) 44(91.7)	3(5.3) 54(94.7)	0.53
Phototherapy Yes No	12(25) 36(23)	20(35) 37(65)	0.26
Continuous positive airway pressure (CPAP) Yes No	7(14.6) 41(85.4)	8(14) 49(86)	0.93
Hood oxygen mask Yes No	22(45.8) 26(54.2)	29(50.8) 28(49.2)	0.60
Umbilical catheter Yes No	5(10.4) 43(89.6)	7(12.3) 50(87.7)	0.47
Packed cell transfusion Yes No	32(66.6) 16(33.4)	34(59.7) 23(40.3)	0.45
Fresh frozen plasma transfusion Yes No	7(14.6) 41(85.4)	11(19.3) 46(80.7)	0.52
Apgar score of the first minute <7 7-10	14(29.1) 34(70.9)	16(28) 41(72)	0.90
Apgar score of the fifth minute <7 7-10	8(16.6) 40(83.4)	8(14) 49(86)	0.70
Total parenteral nutrition Yes No	29(60.4) 19(39.6)	37(64.9) 20(35.1)	0.37

Ranitidine treatment Yes No	 37(77) 11(23)	 47(82.5) 10(17.5)	0.49
Third-generation cephalosporin treatment Yes No	 19(39.6) 29(60.4)	 15(26.3) 42(73.7)	0.08
Vancomycin treatment Yes No	 36(75) 12(25)	 36(63.2) 21(36.8)	0.20
Meropenem treatment Yes No	 31(64.6) 17(35.4)	 29(50.8) 28(49.2)	0.15

* Significant correlation.

Table-3: Health outcome in hospitalized newborns with and without fungal colonization (n=105)

Variables	Outcome			P-value
	Discharge Number (%)	Improvement Number (%)	Death Number (%)	
Cases with fungal colonization, n=48	23(47.9)	9(18.8)	16(33.3)	0.02
Cases without fungal colonization, n=57	41(72)	8(14)	8(14)	

4- DISCUSSION

In this prospective study, we screened 105 newborns in the NICU for fungal colonization; the prevalence rate was 45.7%. This finding is higher than the data reported in a literature review of fugal colonization occurring in NICU setting (8, 14, 15). Benjamin et al., described the profile of fungal colonization with a prevalence of 68%; this high rate is in preterm neonates weighing less than 1500g admitted to NICU.[16]In a multicenter cohort study of six NICUs, Saimanet al., showed the prevalence of 23% (486 of 2157 infants) for candida spp. colonization in New York, USA (16). Farmaki et al. reported the rate of 12.1% fungal colonization in the NICU of Greece and Ali et al. revealed 12.8% candida colonization among 102 preterm newborns in Saudi Arabia (8, 18); lower rates are probably due to small surveillance fungal cultures from the mouth, rectum, and trachea in Greece and the mouth, umbilicus and anus in a further study.

The variation of fungal colonization strongly depends on hand hygiene, the use of routine antifungal and antiseptic measures applied in NICU setting (18). Fungal colonization was unrelated to gestational age, newborn's age, birth weight, gender and duration of ICU admission. In contrast to our study, Saiman et al., showed that birth weight ≤ 1000 g and gestational age < 32 weeks were associated with fungal colonization (17). The level of hemoglobin tends to be a risk factor for the development of fungal colonization in our study ($p = 0.04$). Fletcher et al., found patients with iron deficiency anemia are at higher risk for growth of candida due to impaired lymphocyte function (20). Chandra and Grace reported that iron deficiency anemia leads to impairment of lymphocyte response to mitogens and antigens, it also prevents polymorphonuclear leukocytes for efficient killing of ingested fungi (21). Although we did not have the facilities to check for type of anemia related to amount of hemoglobin, anemia possibly via

decreased immune defense increased the fungal colonization. This study demonstrates an inverse correlation between endotracheal intubation and fungal colonization. Among 9 studied newborns with endotracheal intubation, only one case (11.1%) presented with fungal colonization. It is reported that endotracheal fungal colonization is present in approximately 6.5% of full-term and 8.3 to 11% of low-birth-weight (LBW) intubated infants (22, 23).

This study found a number of variables that were not associated with fungal colonization, including premature rupture of membranes, NEC, phototherapy, catheters, total parenteral nutrition, broad-spectrum antibiotics, Apgar score, and blood transfusion. It is recommended that these factors should be considered in a sample of large hospitalized infants in NICU. The presence of cardiac disease in the recruited hospitalized newborns established a causal relationship with fungal colonization. High colonization may occur in critically ill infants with cardiac disease due to the increased physical assessment of the newborn, more handling of central and peripheral intravenous lines accompanied with numerous drugs administration.

We suggest that newborns with cardiac disease are likely to benefit from prophylaxis of fungal treatment in NICU. PDA was the most commonly observed disease in our newborns, there are reports of influence of infection on risk of late ductal closure or closure failures in the patients with PDA (24). Candida spp. constitutes the bulk of fungi reported in NICU patients; their species distribution has been shown to be various in different geographical areas. The present study showed candida albicans was the most frequent (54.3%) fungi, followed by candida parapsilosis 34 (24.3%), candida famata11 (7.9%), candida glabrata 10 (7.1%), and candida kefyr 9 (6.4%).

In a study on preterm babies admitted to NICU in India, Mendiratta et al. have reported isolation of candida albicans (45.9%) followed by candida glabrata, candida tropicalis (21.6% each), and candida parapsilosis (8.1%) (25). The incidence of vaginal fungal colonization has been reported to be 25 to 46% during pregnancy in which 85 to 90% occur due to candida albicans (26, 27), therefore, treatment of pregnant women may decrease the vertical transmission of this fungi to the fetus delivered. Candida colonization is also acquired horizontally from the hands of the health care workers particularly for candida parapsilosis (28), so careful attention to hand washing is needed in NICU setting. The rate of candidemia was 0.95% (1 in 105) in the studied newborns which is lower than the data reported in Asia (4–7.7%) and Europe (1.1–1.3%) (29-31).

Our single male newborn with candidemia had a birth weight of 1000 g, gestational age of 30 weeks, colonization of candida albicans in the throat, anus and blood as well as hemoglobin 9 g/dL. However, colonization is distinct from infection, and most colonized patients do not become ill with fungal infections. The observed prevalence of cesarean section in our study was 74%; some authors described that neonates born by cesarean section are at less risk for early colonization than those delivered vaginally, in contrast to the results of our study (6, 8). In this study, we collection the samples from seven sites (the perineum, throat, urine, nose, eye, umbilicus and blood); the most affected colonization sites were perineum 40%, throat 21.4% and urine 17.9%. Similar to our study, others have indicated the throat and perineum as dominant surveillance cultures (32). The majority of our patients (96.7%) had colonization within the first 72 h in the NICU, indicating that new colonization had occurred in a minority of patients after this time. One study reported

that initial screening in the first week of hospitalization detected 10% of the cases, and 64% of them were missed for up to 4 weeks (33). This study showed the rate of death is 3 times higher in hospitalized infants with fungal colonization vs. non fungal infected newborns. Preventing fungal colonization by increasing awareness about the high incidence of fungal colonization among pregnant mothers and encouraging the NICU staff for precise hand washing leads to better outcome of the newborns.

4-1. Study Limitations

A potential limitation of this report was its one center study but it could be employed to minimize disparities in diagnostic tests, result of fungal cultures and therapeutic decision making.

5-CONCLUSION

Based on the results, the prevalence of fungal colonization in NICU hospitalized newborns was 45.7 percent. Candida spp. has been proved to be the most frequent fungi in NICU; the level of hemoglobin and cardiac disease in the newborns had correlation with fungal colonization. The rate of death was is 3 times higher in hospitalized infants with fungal colonization vs. non fungal infected newborns.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENTS

This work was supported by a grant from Shiraz University of Medical Sciences (grant number 9911). The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

8- REFERENCES

1. Chen IL, Chiu NC, Chi H, Hsu CH, Chang JH, Huang DT, Huang FY. Changing of bloodstream infections in a medical center neonatal intensive care unit. J Microbiol Immunol Infect. 2017; 50(4):514-20.

2. Calley JL, Warris A. Recognition and diagnosis of invasive fungal infections in neonates. J Infect. 2017; 74 Suppl 1:S108-S113.

3. Kelly MS, Benjamin DK Jr, Smith PB. The epidemiology and diagnosis of invasive candidiasis among premature infants. Clin Perinatol. 2015; 42(1):105-17.

4. Kaufman D.Fungal infection in the very low birthweight infant.CurrOpin Infect Dis. 2004; 17(3):253-259.

5. Segal, E., A. Soroka, A. Schechter. Correlative relationship between adherence of Candida albicans to human vaginal epithelial cells in vitro and candidal vaginitis. Sabouraudia. 1984; 22(3):191-200.

6. Pinhat EC, Borba MG, Ferreira ML, Ferreira MA, Fernandes RK, Nicolaou SK, ,et al. Fungal colonization in newborn babies of very low birth weight: a cohort study.J Pediatr (Rio J). 2012; 88(3):211-16.

7. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, et al. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group.Pediatr Infect Dis J. 2000; 19(4):319-24.

8. Farmaki E, Evdoridou J, Pouliou T, Bibashi E, Panagopoulou P, Filioti J, et al. Fungal colonization in the neonatal intensive care unit: risk factors, drug susceptibility, and association with invasive fungal infections.Am J Perinatol. 2007; 24(2):127-35.

9. M Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization.Pediatrics. 2006; 118(6):2359-64.

10. Benjamin DK Jr, Stoll BJ, Gantz MG, Walsh MC, Sánchez PJ, Das A, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010; 126 (4):e865-73.

11. El-Masry FA, Neal TJ, Subhedar NV. Risk factors for invasive fungal infection in neonates.ActaPaediatr. 2002; 91(2):198-202.

12. Jordán I, Hernandez L, Balaguer M, López-Castilla JD, Casanueva L, Shuffelman C, et al. C. albicans, C. parapsilosis and C. tropicalis invasive infections in the PICU: clinical features, prognosis and mortality. Rev Esp Quimioter. 2014; 27(1):56-62.

13. Sutcu M, Salman N, Akturk H, Dalgıc N, Turel O, Kuzdan C, et al. Epidemiologic and microbiologic evaluation of nosocomial infections associated with Candida spp in children: A multicenter study from Istanbul, Turkey.Am J Infect Control. 2016; 44(10):1139-43.

14. Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT, et al. National Epidemiology of Mycoses Study Group.Risk factors for Candida species colonization of neonatal intensive care unit patients.Pediatr Infect Dis J. 2001; 20(12):1119-24.

15. Ali GY, Algohary 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 in transmission of disease. J Matern Fetal Neonatal Med. 2012; 25(6):789-95.

16. Benjamin MD, Jolivet E, Desbois N, et al. [Fungal colonization in preterm neonates weighing less than 1500g admitted to the neonatal intensive care unit].Arch Pediatr. 2016; 23(9):887-94.

17. Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT, et al. National Epidemiology of Mycoses Study Group. Risk factors for Candida species colonization of neonatal intensive care unit patients.Pediatr Infect Dis J. 2001; 20(12):1119-24.

18. Ali GY, Algohary 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 in transmission of disease. J Matern Fetal Neonatal Med. 2012; 25(6):789-95.

19. Ramasethu J. Prevention and treatment of neonatal nosocomial infections. Matern Health Neonatol Perinatol. 2017; 3: 5.

20. Fletcher J, Mather J, Lewis MJ, Whiting G. Mouth lesions in iron-deficient anemia: relationship to Candida albicans in saliva and to impairment of lymphocyte transformation. J Infect Dis. 1975; 131(1):44-50.

21. Chandra RK. Grace A. Goldsmith Award lecture. Trace element regulation of immunity and infection. J Am Coll Nutr. 1985; 4(1):5-16.

22. Blum M, Elian I. Tracheal aspirate screening for the detection of intrauterine or intrapartum candidiasis in the newborn.Mykosen. 1978; 21(4):95-8.

23. Rowen JL, Rench MA, Kozinetz CA, Adams JM Jr, Baker CJ. .Endotracheal colonization with Candida enhances risk of systemic candidiasis in very low birth weight neonates.J Pediatr. 1994; 124(5 Pt 1):789-94.

24. Gonzalez A, Sosenko IR, Chandar J, Hummler H, Claure N, Bancalari E. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighing 1000 grams or less. J Pediatr. 1996; 128(4):470-8.

25. Mendiratta DK1, Rawat V, Thamke D, Chaturvedi P, Chhabra S, Narang P.Candida colonization in preterm babies admitted to neonatal intensive care unit in the rural setting.Indian J Med Microbiol. 2006; 24(4):263-67.

26. Gugnani HC, Nzelibe FK, Gini PC, Chukudebelu WO, Njoku-Obi AN.Incidence of yeasts in pregnant and non-pregnant women in Nigeria.Mycoses. 1989; 32(3):131-35.

27. Whyte RK, Hussain Z, deSa D. Antenatal infections with Candida species.Arch Dis Child. 1982; 57(7):528-35.

28. Reissa E, Lasker BA, Iqbal NJ, James M, Arthington-Skaggs BA. Molecular epidemiology of Candida parapsilosis sepsis from outbreak investigations in neonatal intensive care units. Infect Genet Evol. 2008; 8(2):103-9.

29. Caggiano G, Lovero G, De Giglio O, Barbuti G, Montagna O, Laforgia N, et al.

Candidemia in the Neonatal Intensive Care and Analysis of Literature Data. Biomed Res Int. 2017; 2017: 7901763.

30. Rodriguez D, Almirante B, Park BJ, Cuenca-Estrella M, Planes AM, Sanchez F, et al. Barcelona Candidemia Project Study Group.Candidemia in neonatal intensive care units: Barcelona, Spain.Pediatr Infect Dis J. 2006;25(3): 224-29.

31. Al-Sweih N1, Khan Z, Khan S, Devarajan LV.Neonatal candidaemia in Kuwait: a 12-year study of risk factors, species Unit: A Retrospective, Observational Survey spectrum and antifungal susceptibility.Mycoses. 2009; 52(6):518-23.

32. Lau AF, Kabir M, Chen SC, Playford EG, Marriott DJ, Jones M, et al. Candida colonization as a risk marker for invasive candidiasis in mixed medical-surgical intensive care units: development and evaluation of a simple, standard protocol. J ClinMicrobiol. 2015; 53(4):1324-30.

33. Rao S, Ali U.Systemic fungal infections in neonates.J Postgrad Med. 2005; 51Suppl 1: S27-9.