

Clinical spectrum, management and outcome of neonatal candidiasis

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Abstract

Objective: To identify clinical spectrum, management and outcome of neonatal candidiasis.

Methods: The retrospective study was conducted at the Shifa International Hospital, Islamabad, Pakistan, and comprised microbiological records of all the babies admitted to the Neonatal Intensive Care Unit from January 2009 to January 2014 that were reviewed to identify those with positive candida cultures. Medical records were analysed for demographic and clinical spectrum features, management and outcome. SPSS 16 was used statistical analysis.

Results: Of the total 1550 neonatal admissions, 560 (36%) had positive cultures, and, of them, candida was isolated in 49(8.8%) neonates. Among them, 13(26%) had candida albicans and the rest had candida species. Majority were males 34(70%), and preterm with 30(61%) being <37 weeks. The mean birth weight was 2000±873 grams. Mean age at admission was 6±7.6 days. Overall, 39(80%) had ≥2 risk factors. The commonest site of isolation was blood in 41(84%). Besides, 32 (65%) received fluconazole alone for treatment. Mean duration of anti-fungal therapy was 10±5 days (range: 1-21 days). Twelve (24%) neonates expired and the cause of death was candida sepsis in 10(20%) cases. Mortality was not significantly associated with gender, place of birth, gestation, risk factors, length of stay, prior antibiotic exposure or receipt of antifungal prophylaxis except those who were ≤1500 grams ($p<0.05$).

Conclusion: Approximately one in ten at-risk neonates may develop candida sepsis with high mortality. Early institution of anti-fungal therapy may prove to be life-saving.

Keywords: Candida albicans, Sepsis, Neonate, Anti-fungal. (JPMA 65: 1206; 2015)

Introduction

Candida (C.) species are common pathogenic isolates in neonatal intensive care units (NICUs) with increasing prevalence.¹⁻⁵ Invasive candidiasis cause high morbidity and mortality in neonates, especially in premature neonates. Risk factors include early fungal colonisation, antibiotics exposure, parenteral nutrition, necrotising enterocolitis and invasive procedures such as central venous catheters. A high index of suspicion in neonates at high risk for candidal sepsis and early institution of anti-fungal therapy may prove to be life-saving. There are only few studies on neonatal candidiasis from Pakistan.^{6,7} The current study, as such, was planned to assess a single-centre experience and outcome of premature neonates with invasive candidiasis.

Material and Methods

The retrospective study was conducted at the 20-bed NICU of Shifa International Hospital (SIH), Islamabad, Pakistan. Microbiological records of neonates from January 2009 to January 2014 were reviewed to identify the babies with positive candida cultures. Fungal culture was performed on Sabourad Dextrose Agar with chloromphenicol and CHROMagar was used to identify candida species.

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Samples were taken from blood, tip of endotracheal tube and urine.

No other media was used simultaneously. Medical records of all the babies with positive candida cultures were then reviewed to collect the relevant data, including demographic and clinical features, risk factors, culture and susceptibility results, management and outcome. Data was analysed using SPSS 16. Frequencies and percentages were calculated for gestational age, gender, place of birth, admitting diagnosis, risk factors, receipt of anti-fungal prophylaxis, sites of isolation, anti-fungal drugs and outcome. Mean and standard deviation were calculated for age, birth weight and duration of anti-fungal therapy. Chi square test was applied to analyse the association of mortality with gender, birthweight, place of birth, gestation, risk factors, length of stay, prior antibiotic exposure or receipt of anti-fungal prophylaxis.

Results

There were a total of 1550 neonatal admissions during the study period and 560 (36%) of them had positive cultures. Candida was isolated in 49(8.8%) neonates with positive cultures (Table-1). Among them, 13(26%) had candida albicans and 36(74%) had candida species (Table-2). Bacterial cultures were performed in all (100%) cases and 22(45%) patients had positive cultures. Klebsiella was the commonest isolate in 6(12%) neonates. Overall, 34(70%) were males; 30(61%) were preterm; mean birth weight

Table-1: Demographics and risk factors for neonatal candidiasis.

	N (%)
Admissions	1550 (100)
Positive cultures	560 (36)
Candida isolated	49 (8.8)
Males	34 (70)
Mean birth weight (g)	2000±873
Mean age at admission	6±7.6 days
Gestational Age	
♦ ≤28 weeks	11 (22.4)
♦ 28-34 weeks	12 (24.5)
♦ 34-36 weeks	7 (14.3)
♦ ≥37 weeks	19 (38.8)
≥2 risk factors*	39 (80)
Mechanical ventilation	41 (83.7)
♦ Duration	121±269 hours
Prior antibiotic therapy	45 (92)
♦ Duration of antibiotics	
<7 days	20 (40.8)
7-14 days	14 (28.6)
>14 days	15 (30.6)
Fluconazole prophylaxis therapy given	6 (12)

*Mechanical ventilation, prior antibiotic therapy and partial parenteral nutrition.

Table-2: Microbiology and outcome.

	N (%)
Source of isolation	
♦ Blood	41 (84)
♦ Endotracheal tube	5 (10)
♦ Urine	3 (6)
Cultures	
♦ Candida albicans	13 (26)
♦ Candida species	36 (74)
Positive Follow-up cultures	10 (20)
Therapy	
♦ Fluconazole	33 (65)
♦ Amphotericin B	5 (10)
♦ Combination (Amphotericin B and fluconazole)	8 (16)
♦ None	3 (6)
Mean duration of therapy	10±5 days

was 2000±873 grams 11(22%) were extremely premature <28 weeks; 19(39%) were born in hospital; sepsis was the leading cause of admission in 21(43%) followed by prematurity with respiratory distress syndrome (RDS) in 12 (24.5%). The mean age at admission was 6±7.6 days; 39(80%) had ≥2 risk factors including prior antibiotic therapy 45(92%), mechanical ventilation 41(83.7%); mean duration 121±269 hours), and partial parenteral nutrition 15(30%). Only 6(12%) received anti-fungal prophylaxis. The commonest source was blood 41(84%) followed by

Table-3: Analysis of different risk factors with mortality.

Risk Factors		Death		P value (Chi square test)
		Yes	No	
Gender	Male	5	10	0.339
	Female	733	27	
Place of birth	Hospital	6	13	0.358
	Others	6	24	
Gestation	≤ 32 weeks	7	16	0.36
	> 32 weeks	5	21	
Birth Weight	≤ 1500 grams	7	10	0.048
	> 1500 grams	5	27	
Risk Factors*	≥ Two	11	30	0.389
	< Two	1	7	
Length of Stay	≥ 7 days	7	21	0.92
	< 7 days	5	16	
Length of ventilation	≤ 48 hours	6	21	0.68
	> 48 hours	6	16	
Prior antibiotic exposure	Yes	11	34	0.98
	No	1	3	
Anti fungal prophylaxis	Yes	2	4	0.59
	No	10	33	

*Mechanical ventilation, prior antibiotic therapy and partial parenteral nutrition.

endotracheal tube 5(10%). Overall, 47(96%) had clinical sepsis and 2(4%) had colonisation at the time cultures were taken. Besides, 32(65%) received fluconazole for treatment (Table-2). Repeat culture was performed in 32(65%) babies and 10(20%) of them had second positive blood culture despite anti-fungal therapy. Mean duration of anti-fungal therapy was 10±5 days. Twelve (24%) babies expired and cause of death was candida sepsis in 10(20%) cases. There was no significant difference in those who died versus those who survived in terms of gender, place of birth, gestation, risk factors, length of stay, prior antibiotic exposure or receipt of antifungal prophylaxis. However, mortality was significantly high in premature neonates ≤1500 grams (p<0.05) (Table-3).

Discussion

Candida species are important pathogens in neonates admitted to the NICU. It is now the third most common cause of neonatal sepsis and is increasingly being reported across the globe.¹⁻³ The incidence of candidiasis varies among different NICUs from 1.2% to 20.4% with one-quarter reporting rates greater than 13.5%.³⁻⁵ Incidence was similar (8.8%) in our cohort as well with high proportion in <1500 grams. Differences in level of care, number of deliveries and clinical practices, such as the use of broad-spectrum antibiotics may explain this variation. The attack rate is estimated to be 1.48 candidal infections/1000 patient-days in those admitted to the NICU.³ There is a high propensity of candida infections in

extremely low birth weight (ELBW) infants (<1000 gram).^{3,4} In neonates <1000 gram the annual incidence is 5.1 vs 0.42 of candidemia/1000 patient days compared to those neonates with >1500 grams weight.³ A low frequency of 0.9% of candidiasis was noted with greatest incidence (46%) in <1500 grams neonates.⁷

There has also been a shift in species of candida causing neonatal infections. While *C. albicans* account for more than 60% of infections other non-candida *albicans* species are increasing, mostly linked to horizontal transmission.^{2,3,8,9} *C. parapsilosis* is the second most commonly isolated candida species with important implications for empirical therapy.^{3,10} In our study, almost 75% patients had non-*albicans* infections which is unusually high. Unfortunately our lab at that time did not do further candida speciation. A study from Karachi also reported *C. tropicalis* as the commonest (36%) species in their cohort.⁶

Multiple risk factors are associated with neonatal candidiasis.^{4,5,7-10} A larger premature population, indiscriminate use of sophisticated and invasive equipment and procedures, longer hospital stay and indiscriminate use of broad-spectrum antibiotics play a major role. Specific risk factors include gestational age <32 weeks,^{1,5} central venous catheters, intubation or recent surgery,^{4,5,10,11} mechanical ventilation or prolonged NICU stay,⁷ broad-spectrum antibiotics and colonisation.^{3-5,12-14} Nosocomial candidaemia was associated with maternal colonisation (odds ratio [OR] 15.8; 95% confidence interval [CI]: 2.63, 94.77) and the number of sites of candida colonisation (OR 24.02; 95% CI: 1.89, 304) besides other factors.¹⁴ Also to note that the average number of days of antibiotic use, especially the indiscriminate use of third-generation cephalosporin, correlate with the incidence of invasive candidal infections (correlation coefficient 0.7).^{5,12} We found mechanical ventilation, prior antibiotic therapy and partial parenteral nutrition as common risk factors in our cohort, but due to small numbers there was no statistical difference.

Clinically, neonates with systemic candidaemia present as sepsis like picture with symptoms such as lethargy, feeding intolerance, respiratory distress and apnoea.¹⁵ Other manifestations include mucocutaneous candidiasis, catheter-related infection and focal infection of different organs with a poor prognosis. Metabolic derangements, such as persistent acidosis or hyperglycaemia, and thrombocytopenia are suspicious for candidaemia.^{7,16} Once the diagnosis is confirmed, by culture of blood or sterile fluid, it should prompt a thorough evaluation of other organ

involvement. Diagnosis is confirmed by positive cultures of the blood, urine or cerebral spinal fluid (CSF) with or without abnormal fundi examination, echocardiogram and imaging of the liver, spleen and kidneys.

The management of neonatal candidiasis is now challenging because of increasing incidence, especially of non-*albicans* species, and anti-fungal resistance. Systemic anti-fungal agents with or without removal of source are the mainstay of treatment.¹⁷ Immediate removal of infected source such as an abscess, urine catheter and central line decreases mortality rate and increases the clearance rate of systemic infection.¹⁸ Species identification and anti-fungal susceptibility testing must be done if available especially in neonates, for non-*albicans* species, non-responders and those who are immunocompromised to guide therapy.

Common anti-fungal agents used to treat neonatal candidaemia include amphotericin B, fluconazole and the newer echinocandins. Amphotericin B is the most commonly recommended drug in the treatment of systemic neonatal candidal infection.¹⁹ The expensive amphotericin B lipid formulations may be used if toxicity is a problem, but is not superior to conventional amphotericin B. Studies have shown that fluconazole is effective in treating neonatal systemic candidiasis and is thus commonly used as an alternative.²⁰ Compared to amphotericin B it has several advantages such as excellent oral bioavailability, excellent therapeutic body levels, including the CSF, and excellent for urinary tract infection. However, fluconazole-resistant *Candida* species (*C. krusei*, *C. glabrata*, and *C. parapsilosis*) makes it as second choice for neonatal infections except *C. albicans*. The echinocandins may be used for neonatal candidaemia refractory or resistant to amphotericin B.²¹ The nucleoside analogue flucytosine may be used in combination with amphotericin B in neonatal candidal meningitis.²²

The prognosis of systemic candidiasis is poor with mortality of approximately 50%.²³ Because of the risks involved preventive measures are advocated. General measures include hand washing, the use of gloves, use of antiseptics or disinfectants, single room isolation or cohorting, removing or minimising risk factors (use of H2 receptor antagonists, proton pump inhibitors, broad-spectrum antibiotics, steroids and central lines).⁴ Fluconazole may be considered prophylaxis in high-risk neonates (e.g. ELBWs) and with risk factors (systemic broad-spectrum antibiotics or presence of a central venous catheter).¹⁷ Mortality in our cohort was 25% with significantly related to birth weight ≤ 1500 grams.

Our study had some obvious limitations. It is a single

centre study with a relatively small study population. Other than *C. albicans*, further candida speciation was not done.

Conclusion

Approximately one in 10 at-risk neonates, especially prematures with birth weight <1500 grams, may develop candida sepsis. Early institution of anti-fungal therapy may prove to be life-saving but mortality remains high.

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References

1. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002; 110:285-91.
2. Steinbach WJ, Roilides E, Berman D, Hoffman JA, Groll AH, Bin-Hussain I et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. *Pediatr Infect Dis J*. 2012; 31:1252-7.
3. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995-2004. *Pediatrics*. 2006; 117:1680-7.
4. 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; 19:319-24.
5. 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:e865-73.
6. Farooqi JQ, Jabeen K, Saeed N, Iqbal N, Malik B, Lockhart SR. et al. Invasive candidiasis in Pakistan: clinical characteristics, species distribution and antifungal susceptibility. *J Med Microbiol*. 2013; 62:259-68.
7. 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 Dev Ctries*. 2011; 5:216-23.
8. Al-Sweih N, Khan Z, Khan S, Devarajan LV. Neonatal candidaemia in Kuwait: a 12-year study of risk factors, species spectrum and antifungal susceptibility. *Mycoses*. 2009; 52:518-23.
9. Miranda LN, van der Heijden IM, Costa SF, Sousa AP, Sienra RA, Gobara S, et al. *Candida* colonisation as a source for candidaemia. *J Hosp Infect* 2009; 72:9.
10. Zaoutis TE, Greves HM, Lautenbach E, Bilker WB, Coffin SE. Risk factors for disseminated candidiasis in children with candidemia. *Pediatr Infect Dis J*. 2004; 23:635-41.
11. Faix RG, Kovarik SM, Shaw TR, Johnson RV. Mucocutaneous and invasive candidiasis among very low birth weight (less than 1,500 grams) infants in intensive care nurseries: a prospective study. *Pediatrics*. 1989; 83:101-7.
12. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics*. 2006; 118:717-22.
13. Kaufman DA, Gurka MJ, Hazen KC, Boyle R, Robinson M, Grossman LB. Patterns of fungal colonization in preterm infants weighing less than 1000 grams at birth. *Pediatr Infect Dis J*. 2006; 25:733-7.
14. 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; 11:240-5.
15. Bendel CM. Candidiasis. In: Remington JS et al eds. *Infectious diseases of the Fetus and Newborn Infant*, 7th edition. Philadelphia: Elsevier Saunders, 2010; pp1055.
16. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infants: clinical manifestations and epidemiology. *Pediatrics*. 1984; 73:144-52.
17. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 48:503-35.
18. Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? *Pediatrics*. 2000; 106:E63.
19. Butler KM, Rench MA, Baker CJ. Amphotericin B as a single agent in the treatment of systemic candidiasis in neonates. *Pediatr Infect Dis J*. 1990; 9:51-6.
20. Driessen M, Ellis JB, Cooper PA, Wainer S, Muwazi F, Hahn D, et al. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. *Pediatr Infect Dis J*. 1996; 15:1107-12.
21. Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. *J Perinatol*. 2005; 25:770-7.
22. Baley JE, Meyers C, Kliegman RM, Jacobs MR, Blumer JL. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr*. 1990; 116:791-7.
23. Lee BE, Cheung PY, Robinson JL, Evanochko C, Robertson CM. Comparative study of mortality and morbidity in premature infants (birth weight, <1,250 g) with candidemia or candidal meningitis. *Clin Infect Dis*. 1998; 27:559-65.