RESEARCH ARTICLE

Risk factors for candidaemia in neonates with sepsis in a tertiary care hospital in Pakistan

Muhammad Faheem Afzal[1], Efra Abbas[2], Muhammad Haroon Hamid[3], Hina Nasir[4], Akmal Laeeq[5], Asif Hanif[6]

Abstract

Objective: To determine the risk factors for candidaemia in babies admitted to a tertiary care hospital with neonatal sepsis.

Methods: This nested case control study was conducted in the Neonatal Unit of the department of Paediatrics, King Edward Medical University/Mayo Hospital, Lahore, from January 2017 to June 2018. A total of 350 neonates having sepsis according to the clinical case definition were enrolled in this study by non-probability convenient sampling. Blood culture for bacteria on first day and for candida on fifth day was sent. Patients were started antimicrobial therapy as per institutional policy on admission. All patients were followed for risk factors for development of candidaemia. Data was analyzed by SPSS 22.0, Odds ratio and logistic regression was used to determine the magnitude of risk factors.

Results: Among 350 septic neonates, 36 isolates were positive for Candida spp, constituting 10.2% of candidaemia among septic neonates. Necrotizing enterocolitis was found to be the significantly associated risk factor for development of candidaemia.

Conclusion: Necrotizing enterocolitis was found to be an important risk factor for development of candidaemia among hospitalized septic neonates.

Keywords: Candida, Neonate, Candidemia, Risk factors

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Introduction

Neonatal candidaemia is defined as isolation of Candida from blood culture in neonates ≤ 28 days. Candida species are important pathogens in nosocomial blood stream infections (BSIs) in neonatal intensive care units (NICUs) with the reported mortality of 2.4–9.0%.[1] Candidaemia has turned into a growing concern in the NICUs with current advances in critical care and overuse of wide spectrum antibiotics.[2]

The risk factors for candida infection include prematurity, low birth weight, invasive interventions, prolonged use of antimicrobials, H_2 blockers, steroids, prior colonization, total parenteral nutrition, and extended length of stay in the NICU.[3] DNA-based methods are considered the gold standard for the identification of fungal isolates, but clinical laboratories in resource-constrained countries have limited access to expensive molecular techniques. The definitive diagnosis still is based upon identification of candida in the blood.[4,5]

Globally, many researchers have studied the incidence and risk factors for neonatal candidaemia. The authors could find only one study from Pakistan that looked into the risk factors for neonatal candidaemia.[3] Therefore, this study was designed with primary objective to determine the risk factors for candidaemia in babies admitted to a tertiary care hospital with neonatal sepsis, and secondary objective was to ascertain the frequency of neonatal candidaemia among septic neonates.

[1-5]Department of Pediatrics, King Edward Medical University, Lahore, Pakistan; [6]Department of Public Health, University Institute of Public Health, University of Lahore, Pakistan

Correspondence: Muhammad Faheem Afzal. e-mail: mfaheem169@yahoo.com

Patients and Materials

This nested case control study was conducted in the Neonatal Unit of the department of Paediatrics, King Edward Medical University/Mayo Hospital, Lahore, from January 2017 to June 2018. The study was approved by ethical review board of King Edward Medical University, Lahore. This neonatal unit serves as a tertiary care centre for a diverse population and receives neonates not only from affiliated obstetric institutions (Lady Willingdon Hospital, Lahore, and Lady Aitchison Hospital, Lahore) but also from other primary and secondary care hospitals.

A total of 350 neonates were enrolled in this study by non-probability convenient sampling. The sample size was calculated using prevalence of 0.9% candidaemia, 0.05 alpha (α) and 0.008 error (d).[3] Neonates having sepsis according to the clinical case definition: any of the clinical signs and symptoms of poor feeding, irritability, lethargy, apnoea (cessation of breath for >20 seconds) or tachypnoea (respiratory rate>60/min), abdominal distension, poor perfusion (capillary refill time >2 seconds) along with two out of 4 criteria of systemic inflammatory response syndrome (Temperature >38.5^{O}C or <36^{O}C, Tachycardia: Heart rate >160/min, Respiratory rate >60/min, Leukocyte count elevated or depressed for age

or >10% immature neutrophils)[6] were included in the study. Neonatal candidaemia was defined as isolation of Candida from blood culture in a baby with ≤ 28 days of age.[6]

After taking informed consent from parents, patients were enrolled, and demography was recorded. With aseptic measures, 1 ml heparinized blood was drawn for complete blood count. A 2 ml non-heparinized blood was drawn for blood culture, which was sent to Paediatric microbiology laboratory and report was received on 3rd day. Patients were started therapy as per institutional policy on admission. On 5th day of admission, 2 ml non-heparinized blood was drawn for candida and culture bottle was sent to Paediatric microbiology laboratory. Sabouraud GC (Sabouraud Glucose) agar was used to isolate candida. The blood culture was streaked onto the surface of sabouraud agar plate. These plates were incubated aerobically at 35±2^{O}C, with minimum exposure to light both before and during incubation. After sufficient incubation, Sabouraud GC agar was examined for fungal colonies exhibiting typical colour and morphology after 48 hours. On the basis of culture results for candida, the newborns were divided into two groups for risk factor analysis. Neonate with candidaemia was labeled as "case" and without candidaemia was labeled as "control." candidaemia was considered as case because the objective of the study was targeted to find out the risk factors, keeping non-candidaemia as control. During admission, all patients were followed for development of Necrotizing enterocolitis (considered in a child having combination of 1 or more clinical signs (bilious gastric aspirate/emesis, abdominal distention or occult/ gross blood in stool) and 1 or more radiographic findings (pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum), requirement of mechanical ventilation and umbilical catheterization. The duration of pharmacological therapy for >72 hours (Cefotaxime, Amikacin, Meropenum, Vancomycin, Linezolid, Piparacillin/Tazobactam, Tobramycin, Ceftazidime, H_2 receptor blocker, Steroids), duration of hospital stay and outcome were recorded on structured case record form.

Data analysis was performed with the use of statistical software SPSS, version 22.0. Mean ±SD was used for quantitative data. Chi-square test was applied to compare risk factors in neonates with and without candida infection. Odds ratio and logistic regression (conditional forward method) were used to determine the risk factors. P-value ≤0.05 was considered as significant.

Results

Among 350 septic neonates, 36 isolates from 350 neonates were positive for Candida spp-,constituting 10.2% of candidaemia among septic neonates. There was female preponderance (61%) among cases. Among preterm, the frequency of candidaemia was 6(16.7%) in those born between 32-37 weeks. Among low birth weight (1500-2499), the frequency of candidaemia was 8 (22.2%). Out of 9 neonates with necrotizing enterocolitis, 6 (16.7%) developed candidaemia. Umbilical vein catheterization was done in 35 neonates, 5 (13.9%) of the cases developed candidaemia. Seven (19.4%) neonates were having co-infection with both bacteraemia as well as candidaemia. Necrotizing enterocolitis, Piparacillin/Tazobactam >72 hours, duration of hospital stay was a significant risk factor at the univariate level, but on adjusted analysis, only necrotizing enterocolitis was identified as a significant risk factor for development of candidaemia in cases. Mortality among the cases was 2.8% while in controls was 9.6%.

Table-1: Clinical risk factors for candidaemia in neonatal sepsis.

Risk Factors	Cases (36)	Control (314)	p-value	Crude OR (CI)	Adjusted OR (CI)
Male	14(38.9%)	178(56.7%)	0.042	2.06 (1.015–4.168)	
Prematurity	8 (22.2)	91 (29.0)	0.298	0.680 (0.32-1.40)	
33-37 weeks	6(16.7%)	64(20.4%)	0.53	1.34(0.53 – 3.37)	
28-32 weeks	2(5.6%)	27(8.6%)	0.48	1.69(0.38 – 7.51)	
Low birth weight	12 (33.3)	133 (42.4)	0.394	0.7 (0.308-1.59)	
1500 – 2499 grams	8(22.2%)	115(36.6%)	0.12	1.96(0.82 – 4.38)	
1000 – 1499 grams	4(11.1%)	18(5.7%)	0.384	0.59 (0.18 – 1.91)	
Age in days on admission	7.28 ± 7.83	5.2 ± 7.44	0.269	0.71 (0.34-1.44)	
Necrotizing enterocolitis	6 (16.7)	3 (1)	0.000	20.73 (4.93-87.13)	211.809(5.823-7.704)
Prolonged mechanical ventilation	5 (13.9)	30 (9.6)	0.412	1.527 (0.552 - 4.221)	
Umbilical Catheterization	5 (13.9)	30 (9.6)	0.976	1.527 (0.55 - 4.22)	

Table-2: Microbiological & pharmacological risk factors for candidemia in neonatal sepsis.

Risk Factors	Cases (36)	Control (314)	p-value	Crude OR (CI)
Bacteraemia	7 (19.4)	30 (9.6)	0.068	2.285 (0.922-5.660)
Staphlococcus aureus	4 (11.1)	16 (5.1)	0.3	1.17 (0.22-6.14)
Psuedomonas	2 (5.6)	8 (2.5)	0.919	1.10 (0.178-6.85)
E.coli	1 (2.8)	6 (1.9)	0.72	0.67 (0.067-6.64)
Steroids	8 (22.2)	42 (13.4)	0.340	1.85 (0.79-4.33)
H2 Receptor blocker	16 (44.4)	129 (41.1)	0.881	1.15 (0.57-2.29)
Cefotaxime	23 (63.9)	253 (80.6)	0.020	0.427 (0.204 - 0.890)
Amikacin	33 (91.7)	291 (92.7)	0.827	0.869 (0.248 - 3.052)
Meropenem	7 (19.4)	35 (11.1)	0.147	1.924 (0.785 - 4.719)
Vancomycin	9 (25.0)	56 (17.8)	0.295	1.536 (0.685 - 3.445)
Linezolid	1(2.8)	4 (1.3)	0.471	2.214 (0.241-20.367)
Piparacillin/Tazobactam	14 (38.9)	60 (19.1)	0.006	2.694 (1.302 - 5.572)
Tobramycin	8 (22.2)	37 (11.8)	0.076	2.139 (0.908 - 5.041)
Ceftazidime	6 (16.7)	36 (11.5)	0.363	1.544 (0.602 - 3.965)
Metronidazole	3 (8.3)	8 (2.5)	0.059	3.477 (0.88 - 13.74)
Mean Duration of hospital stay	11.69 ±7.13	8.19 ±4.51	0.001	2.98 (1.13-7.89)

(Table-1 & 2)

Discussion

We report 10.2% of candidaemia among septic neonates. This was comparable (9%) with that reported in a previous study conducted by Benjamin et al.[2] However, this was higher from a local study from Karachi[3] and from a neighbouring country China[7] where authors reported a frequency of 0.93% and 1.3% respectively. The other studies from developed countries have reported incidence from1.5% to 15.7%.[8-10] This difference might be due to the fact that authors from these studies reported candidaemia from all admitted cases while here it is reported among septic neonates. This is worth mentioning that a second blood culture was performed on 5th day as per protocol of this study.

The present case controlled study aimed to identify the risk factors for candidaemia among septic neonates. The major risk factors identified were necrotizing enterocolitis, use of piperacillin / tazobactam >72 hours, and duration of hospital stay, but on adjusted analysis, only necrotizing enterocolitis was identified as significant risk factor for development of candidaemia in the cases. The authors believe that temporal relation of development of NEC is after development of candidaemia. Disruption of intestinal mucosal integrity in NEC appears to be a critical factor in facilitating the translocation of intra-intestinal Candida into the bloodstream in these infants.[8] The clinical relevance remained significant after taking into account the duration of hospital stay and necrotizing enterocolitis. This finding is consistent with studies from Barton et al[8] and Hammouda et al.[11]

Candida species are notorious for their capacity to attach to foreign materials (such as invasive and indwelling devices) and form biofilms, which may be associated with high virulence and act as a biological barrier that prevents the penetration of antifungal agents and protects the fungal cells from the host's immune responses. This fact may explain why invasive and indwelling medical devices have been identified as factors consistently associated with increased risk of candidaemia.[12,13] In the current study, umbilical venous catheterization, preterm and low birth weight was not found to be statistically significant risk factors for candidaemia. This study's results were consistent with those of previous investigations[11,14,15] suggesting the same. Risk factors previously reported to be associated with neonatal candidaemia have included intubation,[9,11,16] use of high-level antibiotics, prolonged antibiotic use and preterm birth with low birth weight.[14,15,17] Ariff et al[3] found prolonged ventilation (>7 days), positive bacterial blood culture, and prolonged duration of NICU stay (>7 days) as major risk factors. Chen et al[7] reported central venous catheterization and total parenteral nutrition as significant predisposing factors for the development of candidaemia.

Broad-spectrum antibiotic use has also been described as a risk factor for candidaemia.[18] The widespread use of antibacterial agents may suppress bacterial flora and increase Candida colonization density.[19] However, authors did not find use of broad-spectrum antibiotic as risk factor as in this study. A previous study conducted by Kaufman et al[20] showed that decreased use of carbapenem may be associated with decreased incidence of invasive fungal infections. It has also been reported that prolonged exposure to broad-spectrum antibiotics not only increases the risk of developing neonatal candidaemia[21] but also may be associated with the development of refractory candidaemia.[22]

There are certain limitations in the study. The single center design might have compromised the statistical power of the study. Species identification was not possible due to unavailability of advanced microbiology facilities. The occurrence of candidaemia with escalating antibiotic use could not be determined. Episodes of tracheal intubations were not documented. Since central line catheter is not the usual practice in the facility's nursery, so this could not be determined as a risk factor. Despite of these limitations, this study could be considered contributing valuable information to the body of literature. Strict inclusion criteria allowed authors to remove possible confounders and to enroll every positive fungal sepsis patient, fulfilling case definition. The findings from this study reinforce the need of local guidelines for empiric and prophylactic management of candidaemia especially in very preterm babies who are at risk for NEC in intensive care unit.

Conclusion

Frequency of candidaemia among septic neonates was 10.2%. Necrotizing enterocolitis was found to be an important risk factor for development of candidaemia in hospitalized septic neonates.

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