Original Article

Clinical spectrum and outcomes of neonatal candidiasis in a tertiary care hospital in Karachi, Pakistan

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Abstract

Introduction: Candidal infections are a serious problem in neonatal intensive care units, increasing morbidity and mortality in low birth weight infants in addition to escalating health-care costs. Studies exploring the epidemiology of candidiasis in developing country hospitals are rare. This retrospective case-control study aimed to evaluate epidemiology and risk factors associated with candidiasis in a neonatal intensive care unit in Karachi, Pakistan.

Methodology: Cases (neonates (age < 28days, (n = 45) with NICU discharge diagnosis of candidal sepsis or candidemia between January 1996 and December 2006 were matched with controls (newborns with discharge diagnoses other than the above during the same study period) for gender, gestational age, and admission within 72 hours of admission of an index case. Risk factors were identified and clinical course and outcomes (discharge disposition) described. P-value and match-adjusted odds ratios were calculated.

Results: A frequency of 0.9% candidemia was documented in the NICU. The incidence was highest (46%) in VLBW (< 1500gm). *C. albicans* was the leading causative organism (55%), and neonatal risk factors identified were mechanical ventilation (> 7 days), positive bacterial culture, and duration of hospitalization of > 7 days.

Conclusions: Prolonged ventilation, positive bacterial blood culture, and prolonged duration of NICU stay were the major risk factors associated with newborn fungal sepsis in our center. Presence of antenatal care was a significant protective factor in our subset of neonatal population.

Key words: NICU; neonatal intensive care unit; *Candida*; *C. albicans*; BSI; blood stream infections; VLBW; very low birth weight; candidaemia

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Introduction

Candidiasis in neonatal intensive care units has increased steadily in incidence over the last two decades [1,2]. Although a few reports suggest a gradual decline, most surveillance studies have reported a rising trend. The reported incidence ranges between 1.6% and 9% in very low birth weight (VLBW), and 10% and 16% in extremely low birth weight (ELBW) infants [3] with a clear association with decreasing gestational age [4,5].

Candida species accounts for 9% to 13% of all hospital acquired blood stream infections (BSIs) [6]. The mortality associated with *C. albicans* is reported to be 44% [7] in VLBW infants and 30% to 75% in ELBW infants [1,8-10]. This trend is concurrent with the increasing survival of premature newborns secondary to advancement in intensive care. Preterm, low birth weight babies are more vulnerable to acute fungal sepsis, primarily because of an immature immune system, invasive interventions, and prolonged use of antimicrobials that serve as risk factors for fungal colonization [11]. Preceding colonization is an important risk factor for subsequent dissemination and invasive disease [12-15].

Fungal colonization of the skin, gastrointestinal tract, and respiratory mucosa occurs in 26.7% to 62.5% of sick neonates, usually in the first two weeks of life [13,16]. *Candida* species can spread through vertical transmission from maternal flora or via horizontal transmission from hands of health-care workers. Known risk factors for fungal infection include the use of H_2 blockers, steroids, aminophylline, prior colonization, presence of central lines, prolonged use of broad-spectrum antibiotics, total parenteral nutrition, and extended length of stay in the NICU [7,17,18]. The absence of specific clinical and laboratory criteria coupled with the delay in culturing the organism from body fluids has prompted the use of antifungal prophylaxis in certain

centers [19,20]. Although *C. albicans* remains the most common fungal pathogen isolated from blood and body tissue, recent literature shows an increased prevalence of *non-candida* species [21,22].

Practically all the published literature on candidaemia in intensive care units is from developed countries [4,11,23,24]. This study was conceived with the primary objective to document the epidemiology, clinical course, and specific clinical and biochemical markers that aid in the diagnosis of candidemia. Secondarily, the study aimed to identify maternal and perinatal risk factors for the development of candidemia in our setting and discuss our data compared with existing literature from the developed world.

Methodology

Study population and identification

This matched case control study was performed by file reviews of neonates with discharge diagnosis of candidiasis/candidemia/fungal from the neonatal intensive care unit (NICU) at the Aga Khan University Hospital, Karachi, Pakistan, from January 1996 to December 2006.

Cases were identified through two routes: (i) the International Classification of Disease (ICD – 2007) for fungemia, fungal sepsis, and fungal infection (117.0-117.9) was used to retrieve appropriate files; and (ii) a meticulously maintained NICU logbook recording all discharge diagnoses was used to optimize file retrieval. We also reviewed the blood cultures of all cases and controls for final case confirmation. A case was defined as an NICU inpatient with candidal species isolated from blood. A control was matched to a case for gestational age, gender, and time of admission (within 72 hours of admission of an index case). A control was defined as a neonate admitted in NICU whose blood cultures were negative for candidal species.

We identified 45 patients fulfilling case definition during the 10-year period. The number of matched controls was 36.

Serious adverse events following antifungal medication were defined as raised creatinine level (> 1.4 in preterm and > 1.0 in term infants), hematuria, decreased urine output (> 1mL/kg/hr), hypokalemia (potassium < 3 mEq/L), and arrhythmias.

Study setting

The NICU at the Aga Khan University hospital, a tertiary care unit, is a level 111, thirteen-bedded unit (having 12 ventilators) with provision of all neonatal and subspecialty care with the exception of extracorporeal membrane oxygenation and inhaled nitric oxide. Of an average 4,000 in-facility deliveries per year, 11% (450) are referred to the NICU. Average referrals from outside sources are approximately 200 to 250 per year. Premature infants comprise 15% to 20% of the total number of deliveries in the hospital. The unit serves as a tertiary care centre for a diverse population and receives patients from secondary care hospitals from within and outside the city. An empiric antibiotic regime is initiated based on high perinatal risk factors for early onset sepsis. The current hospital antibiotic policy recommends initial empiric use of ampicillin-gentamicin for neonates born within the facility and cefotaxime-amikacin for neonates referred from elsewhere.

Organism identification

The germ tube test (GTT) method was used to differentiate between *C. albicans* and non-*albicans* (NAC) species. Non-*albicans* species were further identified by cornmeal tween agar plates and reading the morphology at 72 hours. API 20C AUX (bioMérieux SA, Lyon France) was used where identification could not be established by the above methods.

Statistical analysis

All collected data was entered in duplicate in FoxPro based data management system (Microsoft Corp 1998, Redmond WA, USA). Key punching errors were rectified and logical errors corrected. Statistical analyses were performed by SPSS version 16 (IBM, NY, USA). The demographic features recorded for cases and controls included postnatal age (PNA) in days, weight (kg/gm), gender, year and date of admission, gestational age (weeks), maternal risk factors (prolonged rupture of membrane, fever, urinary tract infections, lack of antenatal care), APGAR score, antenatal care, history of antibiotics, presence of thrombocytopenia (<150,000/mm^3), and duration of mechanical ventilation. Data was also collected on bacterial cultures (blood, urine, and trachea), length of stay, catheterization (central line and urinary), use of total parenteral nutrition (TPN), types and duration of antibiotics used before positive fungal culture, and discharge disposition. Additional information related to acquired fungal infection including candidal versus
non-candidal, site of isolation (blood, urine, trachea, CSF), duration of antifungal treatment, and

radiological work-up (ultrasound head, abdomen, and echocardiography), were recorded. Continuous variables (age in days, weight in grams, antibacterial therapy, antifungal therapy, TPN duration, and length of stay) were dealt with in means and standard deviation. Categorical variables (gender, poor perfusion (3-5 seconds), abdominal distension, low platelets, and duration of bacterial culture positivity after hospitalization were analyzed as frequencies and percentages. We compared cases and controls among NICU inpatients to identify risk factors associated with acquired candidal infection and the level of significance was set at 0.05. Chi-square tests and Fisher exact tests were applied where necessary. Univariate analysis was performed for all variables and a cutoff of 0.2 was considered significant. Multivariate analysis was performed for those variables that were significant at univariate analysis. The final model was adjusted for confounding. Interactions between biologically plausible independent variables were checked.

Ethical approval

An exemption as granted by the study was approved by the Ethical Review Board (ERB) of the Aga Khan University Hospital, Karachi (1514-Ped-ERC-2010).

Results

Epidemiology and demographic features of study population (Table 1)

Forty-five patients were diagnosed as cases during the study period between 1996 and 2006. This constituted 0.9% of 4,829 neonates admitted during the ten-year period. The frequency of cases per year varied. The highest rate occurred in 2005 (5.9%, n = 22), followed by 2.7% (n = 12) in 2004, and 1.4% (n = 8) in 2006. The incidence of candidemia was highest (46%) among VLBW (< 1500gm) with a male preponderance (71%). Umbilical artery and/or vein catheterization was done in 42% (n = 19) of the cases and 50% (n = 18) of the controls; however, 8% (n = 4) of the cases also had an additional Hickman line. Two (4%) of the cases had indwelling catheters for urine output monitoring. CSF fungal cultures, though not part of the case definition, were sent in 8% (n = 4) of cases and 16% (n = 6) of controls. All were negative. Yield of bacterial (blood, urine, and tracheal) cultures and comparative base line characteristics among cases and controls are shown in Table 1.

Mycology

Eighty-nine isolates from forty-five neonates were positive for *Candida spp. C. albicans* was the leading causative organism isolated in 55% of all cases diagnosed (n = 49 isolates, combining all sites), followed by *C. tropicalis* (21%), and *C. glabrata* (9%). Four cases had duplicate isolates. All cases with *C. parapsilosis* had central lines in place and received total parenteral nutrition (TPN). Table 2 shows the *Candida sub-species* data along with sites of isolation.

Antifungal treatment and adverse events

Sixty-eight percent of the neonates with candidaemia received antifungal treatment (n = 31). Of these, 19 were treated with Amphotericin B, nine with Fluconazole, and three received a combination of Amphotericin and Fluconazole. The average duration of Amphotericin B therapy was 15 days and the mean dose per kg/day was 1.23mg. The average duration of oral Fluconazole was seven days. The mean dose used was 3.85mg/kg/day. Ten cases (22%) did not receive any treatment. In seven of these 10 untreated patients, the reason for deferring treatment could not be ascertained from the records; the other three had cultures reported after discharge with no subsequent follow-up visits.

No serious significant adverse events were documented. There was no unacceptably (two-fold rise) in serum hepatic enzymes or clinical signs of hepatotoxicity and nephrotoxicity, with the exception of one neonate with significantly raised creatinine and renal failure. The electrolytes remained normal during Amphotericin B treatment with creatinine levels of 1.3 mg/dL (preterm 1.3 ± 0.07 and 0.3-1.0 in term infants) before fungal therapy and 0.5 mg/dL after treatment. Similarly, serum potassium remained normal throughout treatment at 4.0 meq/L (5.6 ± 0.5 in preterm and 5.92 ± 0.8 in term).

Risk factors identification (Table 3)

We performed conditional logistic regression analysis. Table 3 shows the crude and adjusted odds ratios of the important risk factors along with their Confidence Interval (CI). We identified lack of antenatal care, mechanical ventilation (> 7 days), concomitant positive bacterial blood culture, and hospitalization (> 7 days) as risk factors for development of candidemia in our cases. Transfusion of blood products was a significant risk factor at the

Table 1. Demographic and neonatal characteristics in cases and controls

Variable	Cases n = 45, (%)	Control n = 36, (%)
Preterm*	32 (71)	26 (72)
SGA*	23 (52)	20 (55)
Weight on admission		
Male*	32 (71)	26 (72)
Age in days (on admission)	12.29 ± 16	3.97 ± 10.45
Weight in grams (on admission)	1792.6 ± 886.53	2041.82 ± 944.45
Born outside our hospital	29 (64)	14 (39)
Received antenatal care	30 (66)	31 (88)
Mode of delivery (SVD)	25 (55)	21 (60)
Maternal factors		
• PROM	9 (20)	2 (5)
• Fever	6 (13)	1 (3)
• UTI	5 (11)	2 (5)
• GDM	4 (8)	3 (8)
• HTN	7 (15)	4 (11)
Neonatal factors		
• Required mechanical ventilation	32 (71)	25 (69)
• Days on mechanical ventilation	19 ± 15	5.2 ± 4
• Intubation >2 times	16 (35)	5 (14)
• Catheterizations of vessels **	23 (51)	18 (50)
Signs of sepsis		
• Lethargy	28 (62)	8 (22)
• Abdominal distention/gastric aspirates	20 (44)	4(11)
• Thrombocytopenia	27 (60)	6 (17)
TPN duration in days	20.9 ± 13.5	13.2 ± 14.6
Bacterial culture positivity		
• Blood	29 (64)	10 (27)
• Tracheal	14 (31)	3 (8)
• Urine	8 (18)	2 (5)
Anti-bacterial therapy received (in days)		
• Ampicillin	8.6 ± 5	13.2 ± 14
• Gentamycin	6.4 ± 4	5.3 ± 3
• Claforan	10.3 ± 7	5 ± 2
• Amikacin	12.2 ± 8	8.1 ± 6
• Meropenem	11.8 ± 7	9.3 ± 6.5
• cloxacillin	6.4 ± 5	5.8 ± 4
Duration of hospitalization (in days)	30.8 ± 19.33	19.2 ± 20.10
Neonatal outcome (died)	11 (24)	6 (13)

*Cases & Controls were match on prematurity, SGA and gender
**Umbilical vessels and/or other central venous access

Table 2. Isolates of *Candida* sub-species with sites of isolation

	Blood	Urine	Trachea	Total	Mortality
Candida Albicans	27	19	3	49 (55)	6/24 →0.25
Candida Tropicalis	10	8	1	19 (21)	2/12 → 0.16
Candida Glabrata	3	5	--	8 (9)	1/6 → 0.16
Candida Parapsilosis	2	3	--	5	
Candida Pediculosa	4	--	--	4	
Candida Guiliermondil	1	--	--	1	
Candida Rugosa	1	--	--	1	
Candida Humicola	1	--	--	1	
Candida Krusei	1	--	--	1	

Total number of isolates → 89

univariate level but was found to be insignificant on adjusted analysis. Table 4 shows the conditional logistic regression analysis.

Outcomes

Mortality among our candidal sepsis cohort was 24% (n = 11); 40% of expiries had *C. albicans* isolates in blood, while 30% had *C. tropicalis*. *C. parapsilosis* was isolated in four neonates. Of the four neonates with *C. Parapsilosis* infection, three had central lines in place and received total parenteral nutrition.

Discussion

Reporting of fungal blood-stream infection and the spectrum of species involved are essential measures in any intensive care unit in order to implement appropriate preventive and therapeutic strategies [26]. We report a frequency of 0.93% of neonatal candidaemia, which is comparable to the incidence reported from developed countries 1.6% to 5% [9,11,17].

Major clinical markers of neonatal candidemia reported in the literature include temperature instability and thrombocytopenia. We did not record any significant episodes of hypothermia or hyperthermia; however, thrombocytopenia (platelet count < 150,000/$mm^{3)}$) was a consistent finding in our neonatal fungal cohort with an adjusted odds ratio of 2.07 (0.22-19.17), which is comparable to results reported in the published literature [22].

C. albicans was the leading causative organism (55%) in our study followed by *C. tropicalis* (21%) and *C. glabrata* (9%). *C. parapsilosis* was isolated in only two neonates. Our findings were different from that reported by Imad *et al.* [22] and others who found increasing rates of non-albicans candida, namely *C. parasipolosis* [27]. *C. parapsilosis* is known to be associated with the use of total parenteral nutrition and central catheters. Observational studies have recorded an association of prolonged duration of candidemia and increased mortality associated with the delayed removal of central lines [28]. In our subset, the duration of parenteral nutrition was short, with an average of two weeks, and catheters removed on the day that the blood cultures were positive for candida species.

The major risk factors identified in our case control study were mechanical ventilation (> 7 days), presence of bacterial blood-stream infection before the diagnosis of fungal infection, and duration of hospitalization. These findings are similar to those reported in earlier studies [11]. There was a significant difference in the rate of bacterial isolates among cases and controls (64% vs. 27%, p = 0.002), further validating the findings reported from developed countries [1,29].

Provision of antenatal care was a protective factor for neonatal candidemia in our identified cohort; however, we were unable to find studies from the developed countries that have evaluated this factor. We hypothesize that the presence of regular antenatal visits may have led to earlier detection and treatment of maternal fungal colonization, resulting in the reduction in neonatal colonization and dissemination.

Antifungal treatment was effective and safe in our neonates. Sixty percent of our cases received antifungal therapy without any significant adverse effects; however, previous studies by Wang *et al.* and Imad *et al*. [10] from developed countries have

Table 3. Antifungal treatment and mortality rates in neonates with candidemia

Antifungal therapy	Alive	Died	p-value	OR (95% - CI)
Amphotericin	19	8	0.482	2.105 (0.475 – 9.338)
Fluconazole	9	6	0.086	3.333 (0.814 – 13.658)
Amphotericin + Fluconazole	3	4	0.155	4.889 (0.851 – 28.079)

*31 patients (69%) received antifungal therapy.

Table 4. Risk Factors for candidemia; crude and adjusted OR

Variables	Cases	Controls	p-value	Crude OR (CI)	Adjusted OR (CI)
Not received antenatal care	15	3	0.044	3.10 (1.002 – 9.594)	3.461 (0.378 – 31.691)
Born at our institute	22	16	0.024	0.351 (0.142 – 0.869)	0.865 (0.152 – 4.931)
TPN duration (>7 days)	15	4	0.051	5.625 (1.052 – 30.133)	
Ventilation (>7 days)	25	8	0.001	7.143 (2.167 – 23.544)	5.126 (0.562 – 46.785)
Intubation (>2 times)	16	5	0.006	5.0 (1.530 – 16.339)	
Bacterial culture					
• Blood	29	10	0.001	4.713	1.933 (0.348 –
• Trachea	14	3	0.142	(1.821 -1	10.729)
• Urine	8	2	0.172	12.198)	
				4.968 (1.301 – 18.969)	
				3.676 (0.729 – 18.535)	
Signs of deterioration					
• Lethargy	28	8	<0.001	7.50 (2.598	17.476 (2.334 –
• Abdominal distension / Gastric aspirates	20	4	0.001	– 21.652)	130.857)
				6.48 (1.939	
• Thrombocytopenia	27	6	<0.001	– 21.126)	
				5.765 (2.142 - 15.518)	
Duration of hospitalization	35	15	0.001	4.9 (1.865 – 23.873)	
Neonatal outcome					
• Died	11	6	0.393	1.618 (0.533 – 4.905)	

shown an increased rate of complications beyond seven days of treatment.

There are certain limitations in our study inherent in a retrospective chart review. We could not manage a 1:1 case-control ratio due to stringent matching criteria. Reasons for anti-fungal treatment deferral in 7 of 10 patients could not be evaluated due to poor documentation. Three out of ten had culture results reported post-discharge and there was a failure to contact them; hence, the clinical outcome of the ten patients remains unknown. Though powered to detect significant risk factors for fungal sepsis, this is a single centre study and could benefit by pooling data from other similarly placed centers in other developing countries.

In spite of these limitations, this study contributes valuable information to the body of literature. To our knowledge, this is the first study from South Asia on the epidemiology of neonatal candidemia. It is a matched case-control study detecting possible risk factors predisposing candidemia in NICU inpatients. Strict criteria for controls were applied to remove possible confounders, such as environmental factors, NICU outbreaks and institutional standards. A retrospective cohort allowed a time-effective analysis of a relatively rare condition over 10 years. Stringent measures were utilized to enroll every positive fungal sepsis patient, fulfilling case definition. Conditional logistic regression analysis was used to calculate the crude and adjusted-odds ratio for risk factor identification.

This is the first local review of candidemia sepsis in NICU settings that identifies epidemiology, frequency, clinical profile and risk factors, and safety profiles of antifungal and clinical outcomes in inpatient newborns. These findings can serve as a template for the development of local guidelines for prevention and appropriate treatment of candidal sepsis in our intensive care unit.

Conclusion

Candidemia in the NICU is associated with a very high mortality, especially with escalating antibiotic use. Major risk factors are prolonged ventilation (>7 days), positive bacterial blood culture, and prolonged duration of NICU stay (>7 days). Antenatal care has a protective impact on neonatal fungal infection in our settings.

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