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RISK FACTORS FOR CANDIDEMIA IN THE NEONATAL INTENSIVE CARE UNIT OF THE PHILIPPINE GENERAL HOSPITAL FROM OCTOBER 2003 TO AUGUST 2006: A CASE-CONTROL STUDY

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ABSTRACT
Candidemia is a major cause of nosocomial morbidity and mortality in neonates. Prompt diagnosis and treatment is crucial. Risk factor analyses have been conducted worldwide, but limited local data are available. This study was conducted to help pediatricians practicing locally decide when to suspect if a neonate has candidemia; therefore, helping them in the judicious use of empirical antifungal therapy.
Objective: To determine if there was a difference in the risk factors among neonates with candidemia and those without it, who were admitted at the Neonatal Intensive Care Unit of the Philippine General Hospital from October 2003 to August 2006.
Methods: Neonates admitted within the mentioned period, surviving at least on the third day of life, and had at least one blood culture on or after day 3 of life were included in the study. A retrospective review of records was performed to identify the presence or absence of known risk factors for candidemia. The outcome of interest was the presence of candidemia. Each variable was analyzed initially using the bivariate analysis chi-square. Cut-off value for inclusion into multivariate analysis was $p<0.25$. Multivariate analysis, through backward elimination, was done to narrow down independent variables (p value for retention <0.25).
Results: One hundred thirty-eight neonates (69 cases and 69 controls) were included. Based on bivariate analysis, patients exhibiting the following characteristics showed increased risk for candidemia: birth weights of 1250 to 1499g (OR: 3.24; 95% CI: 1.04-10.07) and 1500 to 2449g (OR: 3.84; 95% CI 1.31-11.27); pediatric aging < 28 weeks (OR: 1.42; 95% CI: 1.07-8.5) and 28 to 32 weeks (OR: 1.89; 95% CI: 0.74-4.84); central vascular access (OR: 0.52; 95% CI: 0.26-1.03); prolonged broad-spectrum antibiotic use (OR: 2.0; 95% CI: 0.95-4.2); and increased hospital stay (OR: 0.5; 95% CI: 0.24-1.05). Intralipid use was also associated with candidemia, but was excluded due to insufficient data available. In the multivariate analysis, only patients with birth weights of 1500 to 2449g (OR: 3.65; 95% CI: 1.24-10.77) and 1250 to 1499g (OR: 3.24; 95% CI: 1.04-10.07) qualified. A clinical predictive model in diagnosing candidemia was not possible due to insufficient variables available.
Conclusion: Based on the study, infants with lower birth weights (<2500 g) were at most risk for developing subsequent candida infection.

The vast majority of candidemias are nosocomial infection and *Candida sp.* account for between 5 to 10% of nosocomial blood stream infections. Transmission from health care workers to patients has been demonstrated; although, studies also suggest that the source for many candidemias is the patient's endogenous flora.[1] In 2004, the Neonatal Intensive Care Unit (NICU) of the Philippine General Hospital had 56 out of the 7830 had candidemia; and in 2005, 31 out of 7830 neonates.

Nosocomial candidemia has been an increasing problem among high-risk neonates. If left untreated, it has been shown to be one of the predictors of infant morbidity and mortality. Thus, early diagnosis and management is crucial.

Unfortunately, our ability to diagnose this infection remains limited. The gold standard, which is blood fungal studies usually, comes out after a week or two, at the latest. Thus, alternative means to diagnose the condition are being studied.[3]

In our institution, no risk factor analysis has been performed. This type of study could assist us in deciding who among the neonates should be given empiric antifungal agents in order to reduce mortality from this disease entity.

OBJECTIVES

This study was designed to determine if there is a difference in the risk factors among patients with candidemia and those without it, among infants admitted at the Neonatal Intensive Care Unit of the Philippine General Hospital from October 2003 to August 2006. If the results would permit, a clinical predictive model in diagnosing candidemia in neonates will be created.

MATERIALS AND METHODS

Study Design: The study was a case-control study of neonates who satisfied the inclusion criteria and were admitted at the Neonatal Intensive Care Unit of the Philippine General Hospital from January 2004 to December 2005. Through a retrospective review of records of each infant admitted to the NICU for nosocomial candidemia from October 2003 to August 2006, were matched to a control infant who was also admitted within the unit and within the same month.

Study Population: The inclusion criteria for this study included neonates who were admitted at the Neonatal Intensive Care Unit of the Philippine General Hospital from October 2003 to August 2006, who survived at least the third day of life, and had at least one blood culture on or after day 3 of life. Patients who died were also included in the study. A total of 138 neonates (69 cases and 69 in the control group) were included. A description of the profiles of patients with respect to risk factors and demographic variables were done. Identities of subjects were not disclosed and kept confidential.

Data Collection: The list of patients with candidemia was obtained from the microbiology laboratory logbooks. Cases, who also survived at least the third day of life and had at least one blood culture on or after day 3 of life, were matched with controls admitted within the same month and unit. Records and charts of cases and controls were examined for the presence or absence of the risk factors.

Outcomes Measured: The unit of observation for this analysis was the blood culture. We evaluated for birth weight, gestational age, thrombocytopenia, enteral feeding, ventilatory status, intubation, central vascular access, intralipid use, and length of stay for more than 7 days, and multiple or broad spectrum antibiotics use from 7 days before blood culture was obtained. Birth weight and gestational age were evaluated as continuous variables. Gender, feeding, mechanical ventilation status, antibiotic use, intralipid, vascular access, and previous blood cultures were evaluated as categorical variables. The outcome of interest was the first episode of candidemia.

Statistical Analysis with Sample Size Estimate

The sample size was twice the number of patients who fall under the inclusion criteria

and were admitted at the Neonatal Intensive Care Unit of the Philippine General Hospital from October 2003 to August 2006. Cases would refer to patients who fall under the inclusion criteria. They were matched to a control infant admitted within the same unit and within the same month. Each variable was analyzed initially using the bivariate analysis using chi-square. Cut-off value for inclusion into multivariate analysis was $p<0.25$. Then, likelihood ratio test was done to narrow down or eliminate independent variables using backward elimination (p value for retention <0.25). From the final multivariate model, we seek to develop a clinical predictive model, if possible. We based the predictive model on the β coefficients and what we thought would be simple and useful for clinicians. Receiver operator characteristics were analyzed to determine the cut-off value.

RESULTS

The microbiology laboratory recorded 90 neonates from the Neonatal Intensive Care Unit with documented candidemia, from October 2003 to August 2006. Among the 90 neonates, only 69 records were available for evaluation. All of them had their fungal cultures obtained on or after the third day of life. These neonates were equally matched with a control infant born in the same month, admitted in the same unit, and with blood culture done on or after the third day of life. More than half (55%) of the infants were male, and appropriately sized for gestational age (72%, only 1 infant was classified under LGA). Pediatric aging breakdown were as follows: 37% infants were < 28 weeks, 19% were 28 to 32 weeks, 25% were 33 to 36 weeks, 20% were 37 to 42 weeks, and none were more than 42 weeks.

Table 1. Demographic data of study population.

Risk Factors	(+) Candidemia	(+) Bacterial Sepsis
Gender		
Male	38	38
Female	31	31
Pediatric Aging		
< 28 weeks	25	26
28-32 weeks	15	11
33-36 weeks	21	13
37-42 weeks	8	19
>42 weeks	0	0
Birth weight		
<1250 g	25	26
1250-1499 g	15	11
1500-2449 g	21	13
>2500 g	8	19
Size for gestational age		
SGA	22	16
AGA & LGA	47	53
Thrombocytopenia		
yes	49	45
no	20	24
Enteral feeding		
yes	51	48
no	18	21
Intubation with mechanical ventilation		
yes	44	45
no	25	24
Central vascular access		
yes	34	45
no	35	24
Intralipid use		
yes	4	0
no	65	69
Length of stay		
< 7 days	53	43
>/= 7 days	16	26
H2-blocker use		
yes	30	31
no	39	38
Multiple or broad spectrum antibiotic use		
yes	53	43
no	16	26

Bivariate analysis of basic demographics and known risk factors for neonatal candidemia were done using chi square. From this, lower birth weights were strongly associated with candidemia for neonates less than 2500g. It was most significant in neonates whose birth weight was within the range of 1500g to 2449 g (OR: 3.84; 95% CI: 1.31-11.27) and in birth weights 1250g to 1499g (OR: 3.24; 95% CI: 1.04-10.07). For birth weights < 1250g (OR: 2.28; 95% CI: 0.85-6.16), it was also significant but not as much as the previously mentioned birth weights. Decreased pediatric aging was also more likely to develop candidemia especially in those patients equal to or less than 28 weeks (OR: 1.42; 95% CI: 1.07-8.5) and in patients who are 28 to 32 weeks (OR: 1.89; 95% CI: 0.74-4.84). Neonates who require central venous lines (OR: 0.52; 95% CI: 0.26-1.03), with prolonged use of broad-spectrum antibiotics (OR: 2.0; 95% CI: 0.95-4.2), and increased hospital stay (OR: 0.5; 95% CI: 0.24-1.05) were also at increased risk for candidemia, although obtained data showed no significance. Intralipid use was also associated with candidemia but was excluded due to insufficient data available (Table 2).

When we included all the independent variables in table 2 into a conditional logistic regression with backward elimination, only two of the variables were significantly associated with candidemia in this study—birth weight and intralipid use. However, intralipid use was dropped due to insufficient positives on its use (Table 3). Since only one variable was available, a clinical predictive model for subsequent candidemia was not possible.

In the final multivariate model, the following birth weights were significantly associated with the development of candidemia in neonates: 1500g to 2449g (OR: 3.65; 95% CI: 1.24-10.77) and 1250g to 1499g (OR: 3.24; 95% CI: 1.04-10.07) (Table 3).

Table 2. Bivariate Analysis of the Risk Factors for Candidemia.

Variable	Referent	OR	95% CI	p-value
Birth Weight	<1250 1250-1499 1500-2449 ≥2500	2.28 3.24 3.84 Referent	0.85-6.16 1.04-10.07 1.31-11.27	0.103 0.042 0.014
CVP	Yes No	0.52 Referent	0.26-1.03	0.060
Antibiotic Use	Yes No	2.00 Referent	0.95-4.20	0.066
Length of stay	Yes No	0.50 Referent	0.24-1.05	0.066
Intralipid Use	Yes No	Not enough data Referent		
Pediatric Aging	<28 wks 28-32 wks 33-36 wks 37-42 wks	1.42 1.89 3.02 Referent	1.07-8.50 0.74-4.84 0.26-7.76	0.036 0.185 0.688

Table 3. Multivariable Analysis of Predictors of Candidemia

Variable	Category	OR	95% CI	p-value	B
Birth Weight (g)	<1250 (3)	2.00	0.74-5.48	0.172	0.69
	1250-1499 (2)	3.24	1.04-10.07	0.042*	1.18
	1500-2449 (1)	3.65	1.24-10.77	0.019*	1.29
	≥2500 (0)	Referent			

*significant at α=0.05

DISCUSSION

Risk factors for candidemia are well known.[2] They were identified as following: very low birth weight (<1250 g), < 32 weeks, < 5 APGAR score, platelet count, intralipid use, parenteral nutrition, central venous catheters, H2 blockers, intubation, mechanical ventilation, length of stay of more than 7 days, or intake of multiple or broad-spectrum antibiotics (3rd generation cephalosporin or carbapenem).[3, 4, 5, 6, 7, 8, 9]

Risk factors for mortality in candidemia have also been studied and these include severity of illness, isolation of *Candida tropicales,*[10] and malnutrition state.[11]

A case control study of risk factors associated with candidemia in the NICU was previously performed, wherein median durations of hyperalimentation, intravenous fat emulsion, endotracheal tubes, tracheostomies, antibiotic therapy were compared. It was found that exposure was longer in patients compared with controls and that antibiotic therapy was the most strongly and independently associated with candidemia.[5]

The National Epidemiology of Mycosis Survey study group also performed a risk factor analysis for candidemia in NICU patients using a prospective cohort study. Rectal swabs were used to detect fungal colonization and active surveillance to identify risk factors. They found that candidemia was an important cause of late onset sepsis in NICU patients and the incidence of candidemia might be decreased by the judicious use of treatments identified as risk factors and avoiding H2 blockers.[4]

The lack of empirical guideline in neonates, specifically among infants of very low birth weight—weighing <1250 g, and the associated delay in the diagnosis, prompted one study to device a clinical predictive model, which can identify very low birth weight infants at risk for candidemia; thus, making early intervention using an adequate empiric treatment possible. This was known as the *Candidemia Score,* which uses 4 risk factors: thrombocytopenia (2 points), estimated gestational age of < 25 weeks (2 points), estimated gestational age of 25 to 27 weeks (1 point), and cephalosporin or carbapenem use (2 points). These risk factors were found to be significantly associated with candidemia based on their multi-center, retrospective cohort study. [3]

Local studies on candidemia were limited. A retrospective, multi-center study on *Candida* infection in 4 tertiary hospitals in Metro Manila was done. Candidemia was mostly found in extremes of age (<10 years old and > 60 years old). Candiduria was found in 80% of > 50 years old. Common underlying conditions include the following: prolonged antibiotic use, > 20 days hospital stay, intravascular cannula, indwelling foley catheter, and diabetes mellitus.[12] A candidemia profile has been conducted in pediatric and neonatal intensive care units of a local tertiary hospital. Factors which contributed to increased mortality included early gestational age, low birth weight, prolonged hospital stay, as well as, prolonged use of antimicrobials and presence of co-morbidities. An increase in survival is expected among patients in higher age groups. [13]

A clinical predictive model for empirical therapy for neonatal candidemia in very low birth weight infants was created using a multicenter, retrospective, cohort study of neonatal intensive care unit patients in the United States. However, data obtained in this study did not produce enough sample size for us to validate it in our setting since our subjects, with documented candidemia had birth weights of $\leq$ 1250g.

We evaluated data obtained from October 2003 to August 2006 in an attempt to develop a multivariate model and a subsequent clinical predictive model. This clinical predictive model in diagnosing subsequent candidemia will guide local pediatricians in the empirical treatment of Candidemia.

Majority of the controls matched to cases had bacterial sepsis on blood culture (50/69; 72%). The rest were treated as clinical sepsis.

Based on the bivariate analysis, only birth weight of 1250g to 1499g and 1500g to 2449g and pediatric aging of <28 weeks were statistically significant ($p < 0.05$). But to enable us to include more variables in the multivariate model a $p<0.25$ was used. The additional variables included presence of central venous access, prolonged hospital stay of more than or equal to a week, prolonged broad-spectrum antibiotic use, and intralipid use.

The results supported the findings of other studies which showed that the more critical the patient's condition was (more premature, lower birth weight, requires central line, prolonged antibiotic use, prolonged hospital stay, and intralipid use), the more it was prone to develop candidemia. The exception to this

were neonates whose birth weights belong to <1250g, since results showed that they were equally at risk to develop candidemia (25 neonates) and bacterial sepsis (26 neonates).

Thrombocytopenia, although significantly associated with the development of candidemia, especially in the very low birth weight infants in the clinical predictive model and in other studies, was not demonstrated in our study. This suggests that thrombocytopenia is not a sensitive measure to indicate the presence of candidemia in neonates since it can also be found in neonates with bacterial sepsis (cases: 49/138; 35.5% vs. controls: 45/138; 32.6%).

Other variables measured, which were shown to be associated with candidemia in other studies, were also not demonstrated in our study. These include the enteral feeding (cases: 51/138; 37% vs. controls: 48/138; 34.8%), intubation, use of mechanical ventilation (cases: 44/138; 31.8% vs. controls: 45/138; 32.6%), (cases: 49/138; 35.5% vs. controls: 45/138; 32.6%), and H2-blocker use (cases: 30/138; 21.7% vs. controls: 31/138; 22.5%). As with thrombocytopenia, the occurrence of these factors in candidemia almost equaled those with bacterial sepsis.

The limitations of this study include the limited period of time within which the study was conducted. Extending the period of time to conduct the study will enable us to create a bigger sample size, which in turn, can create more statistically sound results. To enable us to create a clinical predictive model tailored to our setting, a bigger sample size was needed.

CONCLUSIONS/RECOMMENDATIONS

The data obtained in this study was insufficient for us to create a clinical predictive model that would help one to decide when to administer empiric antifungal treatment. But based on the available data, patients with birth weights between 1250g to 2449g presenting with known risk factors for candidemia should raise a high index of suspicion for the infection. At present, it is still the discretion of the pediatrician when to give empiric antifungal therapy to a neonate with known risk factors of candidemia, provided that a prior blood fungal culture was done.

RECOMMENDATIONS

It is recommended to increase the sample size by extending the period of time within which to conduct the study. This will enable us to create a clinical predictive model in diagnosing neonatal candidemia in our setting, which can help us in the judicious use of empiric anti-fungal therapy in neonates at risk.

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