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Clinical characteristics of candidemia among neonates in a Children's Hospital in Vietnam: A retrospective study

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ABSTRACT

Objectives: This study examined the prevalence, pathogenic characteristics, and clinical of neonatal candidemia as well as outcomes of disease treatment. *Methods*: This retrospective study was conducted from 2014 to 2019 on 90 neonates diagnosed with candidemia in Vietnam. *Results:* The cases infected with non-*albicans Candida* (NAC) species exceeded those infected with *C. albicans* (72.2% vs. 27.8%). Of the latter, 87.7% were born preterm, and 80% were of low birth weights. Risk factors included the administration of two antibiotics or more (97.8%), the administration of parenteral nutrition (90%), the insertion of central venous

catheters (67.8%), endotracheal intubation (55.6%), the dispensation of parenteral nutrition with lipids (38.9%), abdominal operations (28.9%), and the use of H2 inhibitors (15.5%). All the neonates were sensitive to amphotericin B, and 92.3% were sensitive to fluconazole. All the fluconazole-resistant cases belonged to the NAC group. The mortality rate from *Candida* septicemia was 26.7%, with the rate involving *C. albicans* being higher (41.7%) than that occurring in the NAC group. *Conclusion*: NAC species have been dominant pathogens, which develop resistance to anti-fungal agents and whose prevalence increases over time.

Keywords: Candidemia, Neonate, Risk factors, Vietnam.

1. INTRODUCTION

Candida spp. is one of the most significant causes of infection in neonatal departments, with the pathogens accounting for 11% to 16% of infections and 25% to 60% of mortalities. The most common causative *Candida* agent is *C. albicans*, with this species being responsible for 80% of neonatal infections. However, recent years have also seen an increase in the prevalence of non-*albicans Candida* (NAC) species, such as *C. parapsilosis*, *C. tropicalis*, and *C. glabarta*. In an examination of 22 *Candida* cases that occurred in 2004 at the Department of Neonatology in Children's Hospital 2 in Vietnam, Hai (2006) found that the prevalence of candidemia was 1.02% and that positive blood cultures with *C. albicans* amounted to 50%. Thi's (2015) study on the Department of Rehabilitation at Children's Hospital 1 showed that the overall prevalence of fungal infections in children under 1 year of age was 71.4% and that out of the mortality rate of 73.8%, 57.1% was caused by *C. albicans*. Rare research on neonatal fungal infection has been conducted despite the increasing prevalence of fungal-induced sepsis, the continued high mortality rate due to this condition (Oeser et al., 2014), and the resistance rate of *C. albicans* (Thi, 2015; Ballot et al., 2013; Wang, Xu, and Hsueh, 2016). To address this gap, the current study assessed the situation *Candida spp.*-triggered sepsis in newborns at Children's Hospital 1 in Vietnam. The findings are expected to contribute to the identification of pathogen trends, clinical characteristics, and therapeutic effects.

2. METHODS

Study design and subjects

This retrospective study was conducted on all newborns admitted to Children's Hospital 1 from June 2014 to June 2019 and diagnosed with candidiasis. A total newborn was imported to this study if they have basis of the following inclusion and exclusion criteria:

Inclusion criteria:

- Positive blood cultures with *Candida spp*.

-Children with signs of sepsis, as suggested by a body temperature>37.5°C or <35.5°C, rapid breathing (>60 times/minute), slow breathing (<30 times/minute), tachycardia (>180 beats/minute), bradycardia (<100 beats/minute), lethargy, irritation, abstention, abdominal distention, abnormal discharge, convulsions, severe jaundice, hemorrhage (Goldstein, Giroir, and Randolph, 2005).

Exclusion criterion

- Incomplete medical records.

Data analysis

The following sample characteristics were documented (Kelly, Benjamin, and Smith, 2015; Leibovitz, 2012): Gestational age, Severity Risk factors, such as gestational age, gender, birth weight [Infants with extremely low birth weights (ELBWs) were defined as those with weights ≤1000 g; infants classified as having a very low birth weights (VLBWs) were those weighing <1500 g; and infants regarded as being of low birth weights were those with weights <2500 g.)]

Birth defects

History of abdominal surgery, central venous catheter insertion, endotracheal intubation

Administration of parenteral nutrition, parenteral nutrition with lipids

Administration of H2 inhibitors, antibiotics before fungal infection

Hospitalization >7 days before fungal infection

A chi-square test was conducted to assess the independence of variables, and a t-test was performed to evaluate the relationship between these variables. A p-value of 0.05 was considered statistically significant.

Ethical approval

The research protocol was approved by the Ethics Committee of Children's Hospital 1 before the initiation of the study. Decision No. 127/HĐĐĐ - BVNĐ1 of April 12, 2014 approved the study to conduct this study at Children's Hospital 1.

3. RESULTS

A total of 90 neonates had neonatal candidemia, as diagnosed on the basis of 1,765 blood cultures, and were treated in the intensive ward of Children's Hospital 1. Out of the 90 subjects, 25 were infected with *C. albicans*, and 65 were infected with NAC species. The epidemiological characteristics of these infections are presented in Tables 1 and 2.

Table 1 Epidemiological characteristics and risk factors (N = 90)

	Characteristics	N (%)	*C. albicans* n (%)	NAC n (%)	P
1	*Gestational age (Mean ± SD)*	79 (87.7)	32.9±3.9	31.3±3.7	
	32 – 37 weeks	27 (30.0)			
	28 – <32 weeks	31 (34.4)			0.08[b]
	< 28 weeks	21 (23.2)			
2	Male gender	48 (53.0)	13 (52.0)	33 (50.8)	0.90[a]
3	*Birth weight*				
	LBW	26 (29.0)	6 (24.0)	20 (30.8)	
	VLBW	26 (29.0)	8 (32.0)	18 (27.7)	0.10[a]
	ELBW	20 (22.0)	3 (12.0)	17 (26.1)	
4	Birth defects	27 (30.0)	7 (28.0)	20 (30.8)	0.90[a]
5	Abdominal surgery	26 (28.9)	6 (25.0)	20 (30.8)	0.80[a]
6	Central venous catheter	61 (67.8)	13 (52.0)	50 (76.9)	0.02[a]
7	Endotracheal intubation	50 (55.6)	15 (60.0)	35 (53.8)	0.40[a]
8	Administration of parenteral nutrition	81 (90.0)	23 (92.0)	58 (89.2)	0.60[a]
9	Parenteral nutrition with lipid	35 (38.9)	7 (28.0)	28 (43.1)	0.20[a]
10	Use of H2 inhibitor	14 (15.6)	5 (20.0)	9 (13.8)	0.60[a]
11	Use of antibiotics before fungal infection	88 97.8)	-	-	
12	Hospitalization > 7 days before fungal infection	87 (96.7)	-	-	

[a] Chi-square test; [b] T-test; NAC: non-*albicans Candida*

Table 2 Mean of risk factor duration

Duration	*C. albicans* Mean ± SD	NAC Mean ± SD	P
Central venous catheter	19.3±3.9	28.0±8.1	<0.001[b]
Endotracheal intubation	7.8±4.5	8.1±5.3	0.80[b]
Administration of parenteral nutrition	20.3±7.4	27.1±13.9	0.03[b]
Parenteral nutrition with lipid	20.3±12.9	18.6±11.1	0.70[b]
Use of antibiotics before fungal infection	5.6±1.4	5.6±1.3	0.90[b]
Use of antibiotics	22.4±11.8	30.3±14.8	0.01[b]
Hospitalization > 7 days before fungal infection	23.4±12.8	31.3±14.8	0.01[b]

[b] T-test; NAC: non-*albicans Candida*

Clinical characteristics

The common clinical symptoms observed were lethargy (72.2%), poor food ingestion (52.2%), vomiting (28.9%), the presence of tympanites (27.8%), and abnormal apnea (27.8%). The two *Candida* groups (i.e., *C. albicans*- and NAC-infected subjects) showed no difference in terms of clinical symptoms.

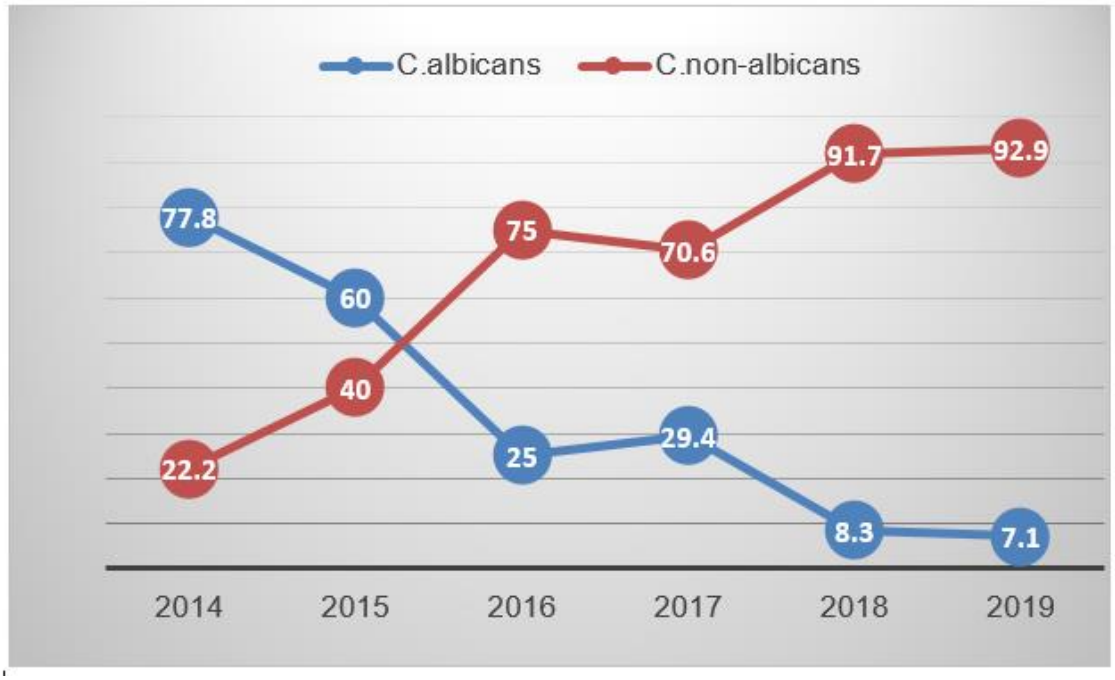

Figure 1 Trends of candidiasis from 2014 to 2019

Leukocytes decreased in 18.9% (17/90) of the cases, but composition increased in 8.9% (8/90) of the subjects. Thrombocytopenia occurred in more than 50% (46/90) of the neonates, and C-reactive protein (CRP) concentration increased in 57.8% (52/90) of the cases. No difference was found between the groups with respect to white blood cell count, platelet count, or CRP concentration (figure 1).

Treatment characteristics

The overall mortality rate caused by candidiasis was 26.7%. The mortality stemming from *C. albicans* reached 41.7%, whereas that induced by NAC species was 21.2%. Amphotericin B and fluconazole were the primary antifungal drugs used to treat neonatal candidemia (table 3).

Table 3 Sensitivity of agents to antifungal drugs

	Amphotericin B	Fluconazole
C. albicans	100%	100%
C. parapsilosis	100%	95.5%
C. tropicalis	100%	100%
C. guilliermondi	100%	100%
C. pelliculosa	100%	100%
C. glabrata	100%	33.3%
C. famata	100%	100%
C. krusei	100%	50%

4. DISCUSSION

Epidemiology

Among the preterm neonates, those with low birth weights accounted for 80%, of which extremely preterm infants (under 28 weeks) made up 23.3%, VLBW babies constituted 29%, and ELBW babies accounted for 22%. The proportion of males was higher than that

of females (1.1: 1). Similarly, Hai (2006) reported that 50% of the newborn infants born in Children's Hospital 2 in 2004 registered low birth weights. In the current work, the infants in the two groups were more than 7 days of age upon admission, and no difference was found with respect to gestational age, birth weight, and age.

Risk factors

Birth defects (30%) were a risk factor for neonate candidemia, and of these conditions, 85.1% were gastrointestinal malformations. Huyen (2003) and Hai (2006) found deformities in 41.9% and 64% of their samples, respectively. In the present study, the occurrence of birth defects due to *C. albicans* and NAC species was similar, amounting to 28% and 30.8%, respectively. In seven cases of congenital malformations owing to *C. albicans*, six were non-rectal and non-Hirschsprung types and one manifested as Down syndrome. The NAC group exhibited 18 cases of esophageal atrophy, duodenal obstruction, intestinal villous atrophy, incomplete intestinal rotation, and abdominal wall opening as well as two cases of peritonitis due to complications from necrotic enteritis. The birth defects occurred mainly in the gastrointestinal tract, which was treated via surgery on the abdominal cavity. The subsequent administration of parenteral nutrition was prolonged because the infants could not be fed orally; hospital stay was equally lengthy, and the use of antibiotics contributed to the increased possibility of fungal infection. No difference was found between the two groups in terms of congenital malformations and abdominal surgery. The same finding was derived in Fu et al.'s (2017) more than four years of study on 69 neonatal candidemia cases.

As regards endotracheal factors, 55.5% of the cases were intubated because of severe clinical, progressive respiratory failure or the administration of anesthesia for surgery. Endotracheal intubation lasted for 8±4 days on average, with the longest spanning 21 days. The rates of intubation in the *C. albicans* and NAC groups were 60% and 53.8%, respectively, but these percentages were derived without consideration for the difference between the groups in terms of the proportion and duration of intubation. According to Saiman et al. (2000), the risk of candidiasis due to intubation (odds ratio = 10.71) was the highest among the risk factors examined by the authors. Fu et al. (2017), Caggiano et al. (2017), and Chi et al. (2011) discovered no difference in intubation-induced infection by *C. albicans* and NAC species, with p-values at 0.17 and 0.11, respectively.

In the present work, 67.8% of the cases (61/90) were inserted with central venous catheters. A difference was found between the two *Candida* groups in terms of the frequency of central venous catheter insertion and catheter retention time. Central venous catheter placement in the NAC group occurred at a frequency 76.9% higher than that in the *C. albicans* group (52%) ($p = 0.02$). The former also registered a longer catheter retention time, averaging at 28 days versus 19 days in the *C. albicans* group ($p < 0.001$). These differences can be explained by the fact that the NAC-infected group had a higher rate of post-surgical gastrointestinal malformations and lower gestational ages and birth weights than did the *C. albicans*-infected subjects. Additionally, it is very difficult to keep the peripheral vein stationary for injection, further contributing to the increase in catheter placement. Hassan et al. (2018), who carried out two years of investigations on 32 neonates afflicted with candidemia, also found a difference in venous catheter retention time between *C. albicans*- and NAC-infected subjects.

A total of 90% of the subjects in the current research were administered parenteral nutrition, with high incidences occurring in both groups (*C. albicans*= 92%, NAC = 89.2%). No significant difference between the groups was found in this respect. However, the duration of parenteral nutrition in the NAC-infected group was 27 days longer than that in the *C. albicans* group (20 days, $p = 0.03$). This result is similar to those of Huyen (2003), Hai (2006), and Thi (2015) (89.7%, 100%, and 83.3%, respectively). The proportion of children receiving venous feeding was high in the present study, similar to Fu et al. (2017) and Caggiano et al. (2017), who reported that 85.5% and 87.8% of *Candida*-infected infants were fed intravenously, respectively, and that the number of neonates fed in this manner in the NAC groups was 90% higher than that of infants fed venously in the *C. albicans* group (71.4% vs.76.7%). The difference was significant ($p = 0.039$) in the case of Caggiano et al. (2017). The major risk factors for *C. parapsilosis* were the insertion of central venous catheters and venous feeding, both of which facilitated biofilm formation on catheters of Caggiano et al. (2017). Therefore, attention should be paid to NAC agents in low-birth-weight infants who are inserted with central venous catheters and stay for long periods in hospitals.

Among the subjects in this study, 35 cases (38.9%) were administered intravenous lipid emulsion. No significant differences between the two groups were found connection with the rate and duration of administered intravenous lipid emulsion. The rate of administered intravenous lipid emulsion in the NAC group was 43.1%, where as that that in the *C. albicans* group was 28% ($p = 0.2$). Those infected with *C. albicans* were subjected to administered intravenous lipid emulsion at an average of 20.3±12.9 days, whereas those infected with NAC species received the therapy for18.6±11.1 days ($p > 0.05$). Intravenous lipids are necessary for long-term parenteral nutrition, but their use should be considered only when a child is suffering from serious infection. On this basis, intravenous lipid administration differs from intravenous feeding. Of the sample, 97.8% were treated with two antibiotics before positive fungal blood culturing. In each group, an average of five to six types of antibiotics were administered, but no significant

differences in the number of antibiotics administered were found. Fu et al. (2017) also noted a high usage of multiple antibiotics before fungal infection in patients infected with *C. albicans* and NAC species. With regard to duration of administration before fungal infection in the present work, the NAC group was provided medication for an average of 30.3±14.8 days, whereas the *C. albicans* group was medicated for 22.4±11.8 days (Fu et al., 2017). Significant differences in the duration of antibiotic treatment before *Candida* infection between the two groups were found ($p = 0.01$) (Fu et al., 2017). Similar to our results, those of Fu et al. (2017) indicated that antibiotics were administered to the NAC and *C. albicans* groups for 38 and 28 days, respectively, and the difference between the two was significant ($p = 0.033$). In Caggiano et al.'s (2017) study, antibiotics were used for over 14 days for a considerable number of patients in the NAC (92.3%) and *C. albicans* (85.7%) groups.

Another risk factor for candidemia is anti-H2 treatment, but in our study, H2 therapy was employed only in cases of abnormal gastric secretion that was caused by issues other than infection, gastrointestinal abnormalities, or reflux after esophageal surgery. We recorded 14 cases (15.5%) treated with H2 antihistamines. Such medications were used for 20% of the *C. albicans*-infected infants but only 13.8% of the NAC-infected neonates. No significant difference was found in relation to this issue ($p = 0.6$). Similar results were obtained by Fu et al. (2017). Prolonged hospital stay is also a risk factor for *Candida* blood infection, with 96.7% of afflicted children having a hospital stay lasting longer than 7 days prior to positive blood culturing. In this research, the average duration of hospitalization before fungal infection was 29.2±14 days. The NAC group stayed in the hospital for an average of 31 days, whereas the *C. albicans* group was admitted for 23 days. The difference between the groups was significant at $p = 0.01$. Basu et al. (2017), Caggiano et al. (2017), Chi et al. (2011), and Fu et al. (2017) showed that hospitalization for NAC infection was longer than that required for *C. albicans*, with the difference being significant at $p < 0.05$. In the current research, the infants with low birth weights were at risk of contracting candidemia because of central venous catheter placement, prolonged venous feeding, prolonged administration of multiple antibiotics, and length of hospital stay. These problems highlight the need to establish long-term methods for identifying NAC agents when diagnosing *Candida* blood infection for appropriate treatment.

Clinical characteristics

The common clinical symptoms among the patients were lethargy, poor food ingestion, abdominal distention, abnormal discharge, apnea, arrhythmia, and changes in body temperature with fever and hypothermia. These symptoms occurred at a higher rate in the *C. Albicans* group (80%) than in the NAC group (69.2%). The following gastrointestinal symptoms also accounted for a high rate of occurrence in both groups: poor food ingestion (44% and 55.4% in the *C. albicans* and NAC groups, respectively), abdominal distention (36% and 24.6%,, respectively), and abnormal discharge (32% and 27.7%, respectively). Respiratory abnormalities, such as apnea, dyspnea, and cyanosis were more common in the NAC group by 30.8%, 29.2%, and 20%, respectively, compared with incidences in the *C. albicans* group. Fever is a typical symptom of sepsis, but both groups exhibited a low incidence of fever (Russell, 2012; Stoll et al., 2002). In the *C. albicans* and NAC groups, hypothermia was more prevalent than fever, occurring in 8% and 21.5% of the patients, respectively. The results showed clinical signs of non-specific infection, similar to those observed with clinical sepsis (Oeseret al., 2014; Benjamin et al., 2000; Puopolo, 2004). The two groups exhibited no difference in the aforementioned symptoms. This trend points to the difficulty of diagnosing neonate candidemia in clinical settings. Nevertheless, in children exposed to many risk factors and exhibiting poor clinical progression despite broad-spectrum antibiotic treatment, assessing the presence of *Candida* agents is also necessary. Diagnosis limits delay in treatment.

Subclinical characteristics

We also documented changes in agent composition in the blood of the patients from 2014 to 2019. In 2014, *C. albicans* was the main infecting agent, accounting for 77.8% of the cases, whereas NAC species accounted for only 22.2%. The annual results indicated that the rate of *C. albicans* infection decreased gradually each year. In 2018, infection from this agent amounted to only 8.3%, and in the first six months of 2019, only one case out of 14 was a candidemia infection (7.1%). In contrast, the rate of NAC infection gradually increased from 22.2% in 2014 to 92.9% in 2019. Ballot et al. (2013) acquired similar findings, with the authors observing an increase in NAC agents. Caggiano et al.'s (2017) research like wise reflected a change in agents from 2007 to 2015, with NAC species increasing gradually. The authors also uncovered that NAC was the predominant agent of Asian candidiasis infection (Wu et al., 2014; Femitha et al., 2013; Chaurasia et al., 2015; Al-Sweih et al., 2009; Wu et al., 2009).

Of all the agents, the most prevalent cause of infections was *C. parapsilosis* (45 cases or 50%), followed by *C. albicans* (25 cases or 27.8%). *C. tropicalis* infection was detected in six cases (6.7%), whereas *C. guilliermondii* was responsible for four infection cases (4.4%). *C. glabrata* and *C. famata* each accounted for three cases (3.3%), and *C. krusei* and *C. pelliculosa* each accounted for two cases (2.2%). Ballot et al. (2013) reported similar results, with *C. parapsilosis* being the principal infecting agent (54.2%), followed by *C. albicans* (27.1%), *C. tropicalis*, and *C. glabrata* (3% and 4%–8.5%, respectively). In Caggiano et al.'s (2017) exploration, *C.*

parapsilosis accounted for the highest proportion of infections (58.5%), followed by *C. albicans* at 34.1% and *C. glabrata* and *C. tropicalis* at 7.4%.

Treatment characteristics

Out of the infants, 88.9% were treated with antifungal medications, whereas seven cases were left untreated because they died before the results of the positive fungal culture were released, and three cases were allowed to go home. Amphotericin B and fluconazole were the primary antifungal drugs used to treat candidemia at Children's Hospital 1. Out of the neonates, 100% were sensitive to amphotericin B, as determined as well by Thi (2015). Other studies recorded similarly high sensitivity to amphotericin B among both *C. albicans*- and NAC-infected cases. We found only five cases (5.6%) of drug resistance to fluconazole, among whom two were infected by *C. parapsilosis*, two were afflicted with infection due to *C. glabrata*, and 1 was a case *C. krusei* infection. Other researchers such as Caggiano et al. (2017) and Chi et al. (2011) noted low rates of fluconazole resistance (1.4% and 3.3%, respectively), whereas Wang et al. (2012) reported no resistance. Basu et al. (2017) noted levels of fluconazole sensitivity of 60%, 60%, and 75% for *C. parapsisolis*, *C. glabrata*, and *C. krusei*, respectively. In contrast, Hassan et al. (2018) showed that *C. parapsilosis*'s resistance to fluconazole was 50% in developing countries. The rate of fluconazole resistance is increasing, especially among the NAC species *C. krusei* and *C. glabrata* (Pemán et al., 2012; Zepelin et al., 2007). Although the current study observed low levels of resistance to this medication, it is important to note that most of the agents that exhibited resistance were NAC species—the type of causative agents that have been gradually increasing in recent years at the Neonatology Department of Children's Hospital 1.

Regarding treatment outcomes, we recorded a neonate candidemia mortality rate of 26.7% (24/90), of which those caused by *C. albicans* reached 41.7%, and those stemming from NAC infection amounted to 21.2%. No difference was found between the two groups. *Candida* is the third most common cause of late neonatal infection with high mortality. In Vietnam, Thi (2015), reported mortality rates of 73.8% (Children's Hospital 1), Huyen (2003), and Hai (2006), reported mortality rates of 46.2%, and 27.2%, respectively in Children's Hospital 2. Other studies recorded low mortality from NAC infections, which were more frequently caused by *C. parapsilosis* than *C. albicans* (Chi et al., 2011; Santolaya et al., 2014; van Asbeck, Clemons, and Stevens, 2009; Benjamin Jr. et al., 2010). The high mortality rate from *C. albicans* infection can be explained by its stronger virulence compared with that of NAC agents (Neves et al., 2017). Out of the *C. albicans* infections in the present work, four resulted in death before the results of fungal culture could be obtained. Therefore, antifungal treatment should be decided early to reduce mortality. Appropriate antifungal agents should likewise be selected, and current antifungal resistance should be identified.

5. CONCLUSION

This study showed that the proportion of *C. albicans*-induced sepsis decreased but that sepsis stemming from NCA agents increased from 2014 to 2019. Therefore, in the future, studies need to be done on NAC agents in order to study more closely NAC agents in the environment of Vietnam. All the cases exhibited sensitivity to amphotericin B, and 92.3% showed sensitivity to fluconazole, study recommend that doctor need to think first this medicine when to be diagnosed with the neonatal candidemia. The prevalence of neonate candidemia was high (26.7%), with mortality rate from *C. albicans* infection being higher than that due to NCA infection. No difference was found between the groups as regards clinical symptoms, subclinical leukocytosis, platelet count, and CRP concentration. There is a need to detect the presence of septicemia agents based on other factors.

Authors' Contributions

Xuan Minh Ngo (Principle Investigator) - Role: Literature Review, Introduction, Methodology, Data Analysis, Results Writing, Discussion, Abstract.

Diem Thi Ngoc Nguyen (Co-Investigator) - Role: Proposal Writing, Introduction, Methodology, Data Analysis, Results Writing and Discussion.

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