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A Decade of Invasive Candida Infection in Neonates: A Retrospective Study at a Tertiary Neonatal Intensive Care Unit in Thailand (2008–2018)

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ABSTRACT

OBJECTIVE: To determine the epidemiology of invasive candida infection in the neonatal intensive care unit (NICU) at a tertiary care center in Thailand over 10 years.

METHODS: A retrospective descriptive study was conducted. Participants were enrolled from all neonates diagnosed with invasive candidiasis infection (ICI) in Vajira Hospital between 2008 and 2018. Demographic data, microbiological results, and neonatal outcomes were reviewed.

RESULTS: During the study period, 9,031 neonates were admitted to the NICU. A total of 14 neonates were diagnosed with ICI, giving a prevalence of 1.5 cases per 1,000 infants admitted to the level II and III NICU. The median (IQR) gestational age and birth weight were 28.5 weeks (27.0, 31.0) and 1,053 g (850.0, 1,586.5), respectively. In all, 10 (71.4%) and 8 (57.1%) neonates had positive blood and urine cultures, respectively. All infants had negative cerebrospinal fluid cultures. Among 14 neonates diagnosed with ICI, 7 (50.0%) neonates had positive cultures for *Candida albicans*. The overall mortality rate of neonates with ICI was 21.4%.

CONCLUSION: ICI exhibits a low incidence rate within Vajira Hospital. This occurrence is demonstrably associated with prematurity, extremely low birth weight infants, and a demonstrably high mortality rate.

KEYWORDS: invasive candida infection, neonates, neonatal intensive care unit

INTRODUCTION

Invasive candidiasis infection (ICI) is a significant cause of sepsis in neonatal units, particularly in neonatal intensive care units (NICUs)[1-2]. ICI is associated with increased morbidity and mortality rates[1,3-4]. Its morbidity includes long-term developmental and neurological sequelae, such as cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia[5-8]. The incidence of ICI in neonates varies substantially between hospitals[5, 9-16]. Established risk factors for neonatal ICI include prematurity, extremely low birth weight (ELBW), invasive procedures such as central venous catheterization (CVC), and broad-spectrum antibiotic exposure[2,5,9,16-19]. For units with an ICI incidence exceeding 10%, the Infectious Diseases Society of America (IDSA) recommends implementing fluconazole prophylaxis in all NICU infants born weighing less than 1,000 grams[20]. This highlights the crucial role of individual unit-level NICU ICI

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incidence data in guiding fluconazole prophylaxis decisions. The aim of this study was to determine the epidemiology of invasive candida infection in the NICU at a tertiary care center in Thailand over 10 years.

METHODS

This retrospective descriptive study was conducted in the level II and III NICU at Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Vajira Hospital is a 900-bed university hospital with approximately 2,000 deliveries per year. We reviewed the medical records of infants diagnosed with candida infection based on the International Classification of Diseases, 10th Revision (ICD-10) codes (B370, 371, 372, 374, 375, 377, 378, 379, and P375). The inclusion criteria included being born at Vajira Hospital between January 2008 and December 2018, and diagnosed with ICI confirmed by the positive isolation (aerobic culture) of *Candida species (spp.)* from blood, cerebrospinal fluid (CSF), or urine obtained via catheterization or suprapubic aspiration. Retrospective data were collected anonymously using a designated form.

Maternal and infant characteristics documented included sex, gestational age (GA), birth weight (BW), delivery route, maternal antenatal care, maternal chorioamnionitis, and Apgar scores. Outcomes data collected included age at diagnosis, source of Candida isolation and species identified, length of hospital stay, and in-hospital mortality. Treatment data included type and duration of antifungal and antibiotic use, ventilation support duration, invasive procedures (e.g., CVC, urethral catheterization), total parenteral nutrition administration, and history of surgery. Ethical approval for the study protocol was granted by the Institutional Review Board of the Vajira Hospital Faculty of Medicine, Navamindradhiraj University (COA093/62).

ICI is defined as an infection confirmed by the isolation of *Candida spp.* from the blood, CSF, or urine, collected through either urethral catheterization or suprapubic aspiration, with microbiology laboratory confirmation. Disseminated candidiasis is defined as more than 1 site of infection confirmed by the isolation of *Candida spp.*

Very low birth weight (VLBW) and ELBW infants are defined as those with a BW less than 1,500 g, and 1,000 g, respectively. Level II NICU (step down or special care baby unit) is defined as units that can take care of infants without advanced respiratory support who need mild support for their immaturity or transitional illness (those on supplemental oxygen or gastric tubing). Level III NICU 3 (tertiary care or Intensive Care) is defined as units that can take care of infants with critical illness, or those on advanced respiratory support.

Descriptive statistics were calculated using the Statistical Package for Social Science software version 22.0 (SPSS Inc., Chicago, IL, USA). Numerical data were analyzed using the mean and standard error of the mean or the median and interquartile range, depending on the distribution of the data. Categorical data were analyzed using percentages.

RESULTS

Between January 1, 2008, and December 31, 2018, 9,031 newborns were admitted to the Vajira Hospital level II and III NICU. Of these, 102 infants were diagnosed with candida infection based on ICD-10 codes. However, only 16 were diagnosed with neonatal ICI confirmed by culture. Two infants' medical records were missing; therefore 14 neonates ultimately met the study inclusion criteria (figure 1). Ten (71.4%) were male, the median GA was 28.5 weeks (27.0, 31.0), and the median BW was 1,053 g (850.0, 586.5). Of these infants, 12 (85.7%) were preterm, 9 (64.3%) were VLBW, and 6 (42.9%) were ELBW (table 1).

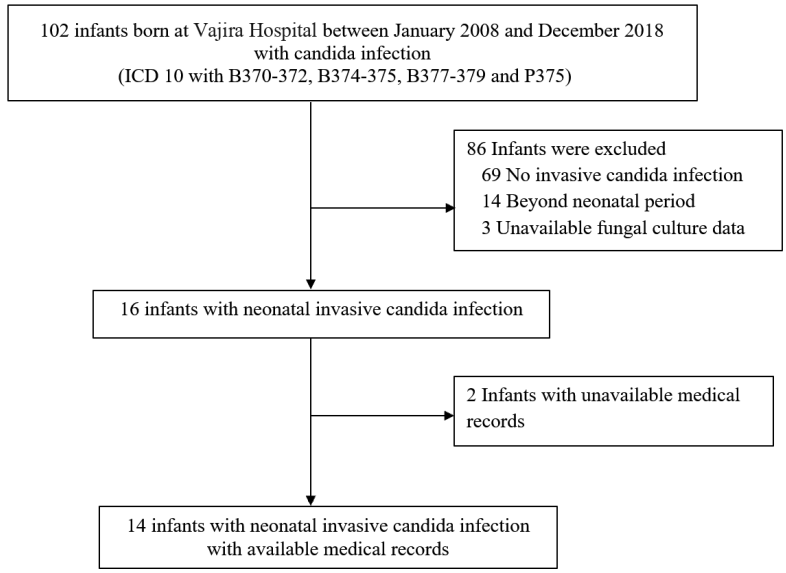

Figure 1 Flowchart demonstrating selection of study

The prevalence of neonatal ICI was 1.5 per 1,000 infants admitted to the level II and III NICU. Among neonates diagnosed with ICI, positive cultures were obtained from only blood in 6 cases (42.9%), only urine in 4 cases (28.6%)–4 cases (28.6%) had both candida septicemia and urinary tract infection. Notably, no infants were diagnosed with candida meningitis. The median age at diagnosis of ICI was 31.5 days (19.0, 44.3) (table 1).

Positive cultures were obtained from blood in 10 cases (71.4%), urine in 8 cases (57.1%), and sputum in 3 cases (21.4%). Of the isolates, 7 (50.0%) were identified as *Candida albicans*, while 7 (50.0%) were *non-Candida albicans species*, (*Candida parapsilosis*, 4 (28.6%); *Candida tropicalis*, 1 (7.1%); unspecified 2 (14.2%). Notably, no positive cultures were obtained from CSF, and no infants were infected with more than one type of *Candida spp.* All *Candida parapsilosis* infections (28.6%) were identified between 2016 and 2018 (table 1).

Nine mothers received antenatal care. Six deliveries were vaginal, while two occurred before arrival at the hospital. One mother was diagnosed with chorioamnionitis (table 1). The infants with ICI were diagnosed with several comorbidities. Necrotizing enterocolitis was present in 5 cases (35.7%), respiratory distress syndrome in 9 cases (64.3%), and bronchopulmonary dysplasia in 10 cases (71.4%) (table 2). All infants received intubation and were administered intravenous medications through a variety of catheters, including umbilical catheters, peripherally inserted central catheters (PICC), and double-lumen CVC (table 1). Additionally, 12 (85.7%) infants were treated with a third-generation cephalosporin and carbapenem (table 2).

Infants diagnosed with ICI received various antifungal regimens: 10 (71.4%) received fluconazole monotherapy, 2 (14.3%) received a combination of fluconazole and amphotericin B, and 2 (14.3%) received amphotericin B monotherapy. The median antifungal therapy duration was 13.0 days (12.0, 14.0) and median hospitalization duration was 89.5 days (42.5, 110.5) (table 2). The mortality rate of infants with ICI was 21.4% (3/14). All fatal cases involved VLBW infants diagnosed with disseminated intravascular coagulopathy (DIC) and septic shock. Two infants (66.7%) who died were ELBW infants (table 2).

Table 1 Maternal and neonatal characteristics with neonatal invasive candida infection (n = 14)

Characteristics	n (%)
Maternal data	
Antenatal care	9 (64.3)
Chorioamnionitis	1 (7.1)
Birth before arrival	2 (14.3)
Vaginal delivery	6 (42.9)
Apgar scores at 5 minutes < 7	3 (21.4)
Neonatal data	
Male gender	10 (71.4)
GA, weeks	28.5 (27.0, 31.0)
BW, g	1,053 (850.0, 586.5)
≥ 1,500	5 (35.7)
1,000-1,499	3 (21.4)
< 1,000	6 (42.9)
Clinical characteristics	
Age at diagnosis of ICI, days	31.5 (19.0, 44.3)
Diagnosis	
Candida septicemia only	6 (42.9)
Candida urinary tract infection only	4 (28.6)
Candida septicemia + urinary tract infection	4 (28.6)
Specimen of positive culture*	
Blood	10 (71.4)
Urine	8 (57.1)
CSF	0 (0)
Sputum	3 (21.4)
Species	
Candida albicans	7 (50.0)
Non-*albicans Candida*	
Candida parapsilosis	4 (28.6)
Candida tropicalis	1 (7.1)
Candida glabrata	0 (0)
Non-specifies	2 (14.2)
Intubation	14 (100.0)
Umbilical vein catheter	14 (100.0)
Central venous catheter (double lumen)	4 (28.6)
Peripherally inserted central catheter	1 (7.1)

Abbreviations: BW, birth weight; CSF, cerebrospinal fluid; g, grams; GA, Gestational age; ICI, invasive candida infection; n, number
Data reported as number and percentage or median and interquartile range.
* Some infants had ≥ 1 specimens of positive culture.

Table 2 The treatment and outcomes of infants with neonatal invasive candida infection (n = 14)

Neonatal outcomes	n (%)
Co-morbidity	
Necrotizing enterocolitis	5 (35.7)
Respiratory distress syndrome	9 (64.3)
Bronchopulmonary dysplasia	10 (71.4)
Antifungal drugs	
Fluconazole only	10 (71.4)
Fluconazole + amphotericin B	2 (14.3)
Amphotericin B only	2 (14.3)
Duration of antifungal treatment, days	13.0 (12.0, 14.0)
Postnatal steroid	1 (7.1)
Total parenteral nutrition	13 (92.8)
Antibiotics use	
3rd generation cephalosporin use	12 (85.7)
Carbapenem use	12 (85.7)
Length of stay, day	89.5 (42.5, 110.5)
Mortality	3 (21.4)

Abbreviations: n, number
Data reported as number and percentage or median and interquartile range (IQR).

DISCUSSION

ICI is a leading cause of mortality and significant complications in neonates. ICI incidence varies between hospitals and is influenced by factors such as GA and BW. This study showed a lower prevalence of ICI (0.15%) in neonates admitted to the level II and III NICU compared with reported rates in European studies (1.1%–3%)[12,21-22] and the United States (0.3%–0.45%)[13,23]. Notably, the incidence of invasive fungal infection in Thai neonates was reported to be 0.8%, with *Candida spp.* identified in 80–90% of cases[16]. This study observed a lower prevalence of ICI among neonates admitted to level II and III NICUs. This finding may be partially explained by the relatively low proportion of VLBW infants admitted to these units in Vajira Hospital. Notably, prematurity and VLBW are established risk factors for ICI development. Therefore, there is no clear justification for fluconazole prophylaxis in all infants with a BW under 1,000 g admitted to Vajira Hospital level II and III NICU.

No cases of candida meningitis were identified among neonates diagnosed with ICI. This observation may be partially attributed to the potential for false-negative CSF cultures. The timing of lumbar punctures in these infants could have been suboptimal, potentially leading to negative results. Notably, antifungal treatment was initiated prior to lumbar puncture procedures, further contributing to the possibility of negative CSF cultures. This practice likely stems from the institutional policy of avoiding lumbar punctures during the intubation process.

Most infants in this study were preterm (85.7%), VLBW (64.3%), and ELBW (42.9%). This finding aligns with a study from tertiary centers in Thailand[10,16], 58.3% premature infants and 63.8% VLBW, but showed a lower prevalence of prematurity (85.7%) and VLBW (64.3%) compared with studies from Europe (87.8% premature infants and 87.8% VLBW) and the United States (94.4% premature infants and 83.1% VLBW)[13,22].

Premature and VLBW infants are at high risk for ICI because of several factors, including candida colonization, impaired gastrointestinal, skin, and immune function, and the virulence of *Candida spp*[24]. Additionally, they are subject to more invasive procedures.

Multiple studies have identified risk factors for intubation, intravenous catheterization, parenteral nutrition, and the use of broad-spectrum antibiotics[2,5,9,16-19,25]. This study observed a trend suggesting a potential association between a higher proportion of infants with ICI and the presence of these factors. However, a tertiary referral center in southern Thailand found a significantly different risk factor: a history of cefoperazone/sulbactam use[16]. In this study, 57.1% (8/14) of infants with ICI had received this medication.

Candida albicans was the most isolated fungal species in this study (50.0%), in line with studies in Asia, Europe, and the United States[10,13,16,22,26]. Notably, all *Candida parapsilosis* infections (28.6%) were identified between 2016 and 2018, similar to report highlighting a recent increase in the prevalence of this species[14,21-22,27-30]. A 2013 study by Pammi et al., reported a 27% prevalence of *Candida parapsilosis* in neonates after 2000[27]. The association of *Candida parapsilosis* with intravenous catheterization, parenteral nutrition, and biofilm formation may contribute to its increased virulence and emergence as a significant pathogen in this population[28,31].

Fluconazole was the most administered antifungal drug in this study, aligning with recommendations from the IDSA[20,32]. Other studies have also reported successful treatment with fluconazole[15] or fluconazole combined with amphotericin B[10,21]. The median duration of antifungal therapy in this study was 13.0 (12.0, 14.0) days, which is shorter than that reported from China and the United States, where it was 21.5 (5.0, 69.0) days and 23 ± 14 days, respectively[14-15]. While no definitive evidence currently exists for optimal antifungal treatment duration[24], IDSA guidance from 2009 and 2016 recommends 3 weeks of therapy after culture sterilization[20,33]. Therefore, the shorter treatment duration observed in our study warrants investigation and may inform guideline development for managing invasive candidiasis in neonates.

In this study, two ELBW infants (< 26 weeks' gestation) succumbed to candida septicemia complicated by septic shock and DIC. This highlights the importance of early detection and intervention for ICI in this vulnerable population. The specific causes of death in these infants, and the role of antifungal drug administration, warrant further investigation to inform strategies for preventing and promptly identifying ICI in ELBW infants.

This study possesses several limitations that restrict the generalizability of its findings. Firstly, the retrospective analysis conducted at a single tertiary medical center limits the applicability of the results to broader populations. Secondly, the data lack crucial details regarding CVC practices, such as the utilization and duration of PICC lines and CVC, as well as their removal following the detection of catheter-related infections. This information is vital for understanding and optimizing catheter management strategies to minimize the risk of ICI in neonates. Additionally, the absence of data on further investigations, including abdominal imaging for the detection of intraabdominal abscesses, hinders the comprehensive assessment of prognosis and management plans for ICI. Furthermore, details regarding treatment, such as organism eradication and the timing of antibiotic and antifungal administration, are missing, limiting insights into potential therapeutic challenges. Moreover, the study lacks data on long-term outcomes, such as growth and development, which are crucial considerations for understanding the full impact of ICI on neonates. Finally, the descriptive study design inherently limited the analysis of factors associated with ICI. The lack of data on infants who did not receive a diagnosis of ICI within the NICU setting precludes the identification of risk factors and comparative analysis. Additionally, the relatively small sample size might have restricted the ability to detect statistically significant associations between variables.

Nevertheless, the study's 10-year timeframe offers valuable insights into the incidence, characteristics, and outcomes of ICI in neonates. It has informed the development of improved neonatal care guidelines for quality improvement, with an emphasis on preventing ICI and facilitating faster diagnosis, through methods beyond symptom-based approaches and culture results, and timely and appropriate treatment.

CONCLUSION

The prevalence of neonatal ICI is low in Vajira Hospital. This occurrence is demonstrably associated with prematurity, ELBW infants, and a demonstrably high mortality rate. While *Candida albicans* remains the most prevalent fungal isolate in ICI, the emergence of non-albicans Candida species is a growing concern.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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DATA AVAILABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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