

THE RISK OF MORTALITY IN NEONATAL INVASIVE FUNGAL INFECTION OVER 29 YEARS

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Abstract: This study aimed to identify the risks factors of mortality in neonatal invasive fungal infection (IFI) during 1989-2017. This is a retrospective case follow-up study from a tertiary hospital in Thailand. On univariable analysis, there were no statistically different risk factors between the non-survival and survival groups. On multivariable analysis, septic shock during onset of infection (adjusted odds ratio = 5.70; 95% confidence interval: 1.08-30.03; $p = 0.04$) was the only significant risk factor of mortality in neonatal IFI. Besides high mortality, daily costs in the hospital were higher in the non-survival group than in the survival group.

Keywords: Candida, fungi, invasive fungal infections, mortality, neonatal sepsis

INTRODUCTION

Invasive fungal infection (IFI) is a worrisome disease especially frequent broad-spectrum antimicrobials or high multidrug resistant infections (Thatrimontrichai *et al*, 2013; *ibid*, 2016; *ibid*, 2017; *ibid*, 2018). IFI has a poor prognosis among neonates, children, and adults as well as mortality and morbidity (Kullberg and Arendrup, 2015). Neonatal candidiasis is associated with high mortality and the increased risk of neurodevelopmental impairment among survivors (Benjamin *et al*, 2006).

The incidence of IFI is high in extreme age group, particularly in low birthweight (LBW) and preterm infants. Preterm and sick term neonates are more susceptible

to sepsis from bacteria and fungi because of their poor immune systems and long-term hospitalization. Incidence rates of candidemia were reported as 2-14 cases per 100,000 persons in population-based studies (Arendrup, 2010; Cleveland *et al*, 2015). The mean rate of candidemia in neonatal intensive care units (NICUs) was 8.8 per 1,000 patient-discharges from 2002 to 2006 (Neu *et al*, 2009). Oral and systemic antifungal prophylaxis can prevent IFI in very LBW (VLBW) and extremely LBW (ELBW) neonates in the NICUs with high incidences of IFI (Austin *et al*, 2015; Cleminson *et al*, 2015; Thatrimontrichai, 2014).

The case fatality rates in all age groups were 40-60% in spite of antifungal therapy (Ruan and Hsueh, 2009; Kullberg and Arendrup, 2015). Case fatality rates of VLBW infants in the prophylactic and control groups from a meta-analysis were 12.9-16.4% and 17.3-18.9%, respectively (Austin *et al*, 2015; Cleminson *et al*, 2015). Death or neurodevelopmental impairment was 73% of ELBW infants with IFI

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(Benjamin *et al*, 2006). Very little information is available on the risk factors in neonatal IFI (Thatrimontrichai *et al*, 2014). We identify the risk factors of IFI in neonates during 1989-2017 in Thailand.

MATERIALS AND METHODS

Study site and subjects

This study was conducted at the NICU of Songklanagarind Hospital, Songkhla, Thailand. The NICU is a level IV, single 15-bed room in a university-affiliated teaching hospital at Prince of Songkla University which is the referral center (inborn and outborn neonates) for 14 provinces of southern Thailand.

This is a retrospective case follow-up study. Subjects were identified from source records of the clinical microbiological laboratory and medical records at Songklanagarind Hospital. All records were reviewed to ensure that all eligible subjects were identified. The medical records of all neonates with IFI obtained at any time during admission to the NICU from January 1, 1989 to December 31, 2017 were included in the study. Exclusion criterion was either incomplete or missing medical record data. Data of the neonatal patients included baseline characteristics, underlying diseases, clinical manifestations, antimicrobials used, and outcomes. The incidence of IFI represented all cases during 1989-2017, in VLBW and ELBW neonates during 2004-2017. The data from 1989 to 2004 were unreliable in the number of VLBW and ELBW neonates.

The study was approved by the Ethics Committee Board of the Faculty of Medicine, Prince of Songkla University (REC. 59-269-01-1).

Definitions

IFI is defined as a positive blood, ce-

rebrospinal fluid, urine or peritoneal fluid culture with fungal infection. Previous surgery, invasive mechanical ventilation, total parenteral nutrition, and central line use that occurred within 7 days before or on the date of taking the culture were included for this study. The criteria for the diagnosis of ventilator-associated pneumonia and central line-associated bloodstream infection followed the Centers for Disease Control and Prevention and National Healthcare Safety Network guidelines for infants <1 year old (Thatrimontrichai *et al*, 2017; CDC and NHSN, 2018a; *ibid*, 2018b). Patients were defined as having septic shock if they had sepsis plus tachycardia, hypotension (gestational age-dependent) or reduced peripheral perfusion evidence and needed vasopressor agents to maintain blood pressure, even after fluid resuscitation (Goldstein *et al*, 2005).

Statistical analysis

The R program was used to develop a database of categorical and continuous variables. Categorical variables were analyzed as frequency and percentage and compared using the χ^2 test or Fisher's exact test. Continuous (nonparametric) variables were analyzed as median [interquartile range (IQR)] and compared using the Mann-Whitney *U* test. All *p*-values are 2-tailed and a *p*-value <0.05 indicated statistical significance. Univariable and multivariable analyses were performed. Independent variables with *p* < 0.2 in the univariable analysis were retained for a forward stepwise multiple logistic regression. The model with the lowest Akaike information criteria (AIC) was judged as the most parsimonious model. The adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with IFI versus the control group.

RESULTS

Between 1989 and 2017, the incidences of IFI in inborn neonates and total NICU admissions were 0.4/1,000 live births and 0.8%, respectively. During 2004-2017, the incidences of IFI inborn neonates and total NICU admissions in VLBW and ELBW neonates were 17.3/1,000 VLBW live births and 2.0%, and 30.2/1,000 ELBW live births and 3.4%, respectively. The median (IQR) onset of neonatal IFI was 20.1 (12.8, 34.0) days after birth.

A comparison of the baseline characteristics and risk factors of neonatal IFI between the non-survival and survival groups are shown in Table 1. Fungemia and *Candida albicans* were the most common source and species, respectively, of IFI in this study (Table 1). There were no significantly different types of fungal organisms or specimens in the non-survival group compared to the survival group (Table 1). On multivariable analysis with the lowest AIC model (3 variables in Table 2), septic shock was the only significant risk factor of mortality in neonatal IFI.

The case fatality rates of IFI in all neonates, VLBW neonates, and ELBW neonates were 31.3% (26/83), 33.3% (12/36), and 29.4% (5/17), respectively. The median (IQR) daily cost during hospital stay in the non-survival group [297.4 (251.8, 461.2) USD, 1 USD \approx 30 baht] was significantly higher than in the survival group [179.8 (126.6, 200.7) USD]. Extra-daily hospital costs (median difference) was 117.6 USD ($p < 0.001$), respectively.

DISCUSSION

The incidence of inborn neonatal IFI in this study was low as well as in VLBW and ELBW neonates. Prophylactic oral or systemic antifungal therapy was possibly not needed in our study because the inci-

dences of IFI in VLBW and ELBW were 2.0% and 3.4% which were lower than in the treatment groups in the meta-analysis (4-6% and 3-4%, respectively) (Austin *et al*, 2015; Cleminson *et al*, 2015). The case fatality rate in all neonatal IFI (31.3%, 26/83) was similar with a Greek study (28.9%, 17/59) (Roilides *et al*, 2004), higher than in two Chinese studies (7.2%, 5/69 and 8.9%, 4/45) (Yu *et al*, 2013; Chen *et al*, 2016), and lower than a study in South Africa (45.8%, 27/59) (Ballot *et al*, 2013). The case fatality rates of ELBW neonates (29.4%, 5/17) were similar with the US study (34%, 47/137) (Benjamin *et al*, 2010) but higher than the Turkish study (7.5%, 26/349) (Ozturk *et al*, 2006; Austin *et al*, 2015). Moreover, there was a high case fatality rate of IFI in VLBW infants (33.3%) compared to the meta-analysis (17.3-18.9%) (Austin *et al*, 2015; Cleminson *et al*, 2015) and the Chinese study (10.4%, 5/48) (Fu *et al*, 2016).

The mortality of IFI from positive blood culture (29.5%, 13/44) was similar to the US study (28%, 19/69) (Benjamin *et al*, 2010) and a Greek study (35.7%, 15/40) (Spiliopoulou *et al*, 2012). However, the mortality of IFI from positive urine culture (37.9%, 11/29) was higher than the US study (26%, 9/34) (Benjamin *et al*, 2010). There were no differences in the other factors between the non-survival and survival groups especially in the recent period and type of species.

Understanding the risk factors of mortality in neonatal IFI is very important because pediatricians and neonatologists must be aware and consider empirical antifungal therapy, close monitoring, and advise the prognosis. The implication that can be drawn from our study is that septic shock was the risk factor. However, the lower birthweight or ELBW neonates, necrotizing enterocolitis, and delayed removal or replacement of central catheters

Table 1
Risks of non-survival in invasive fungal infection.

Risk factor	Non-survival (n = 26), n (%)	Survival (n = 57), n (%)	p-value
Gestational age (GA), (weeks) ^a	32 (29, 37)	32 (28, 38)	0.70
Birthweight, (g) ^a	1,680 (1,048, 3,098)	1,890 (1,025, 2,714)	0.99
Weight on the date of the taking culture, (g) ^b	2,324.8 ± 1,178.2	2,032.0 ± 882.0	0.21
Birthweight compared with GA			0.34
Small for GA	4 (15.4)	7 (12.3)	
Appropriate for GA	21 (80.8)	50 (87.7)	
Large for GA	1 (3.8)	0 (0)	
Vaginal delivery	20 (76.9)	34 (59.6)	0.19
Referral neonate	17 (65.4)	32 (56.1)	0.58
Male	14 (53.8)	34 (59.6)	0.80
Underlying disease before taking culture			
Neurologic sequelae, congenital or acquired	3 (11.5)	4 (7.0)	0.67
Cardiovascular disease	13 (50.0)	18 (31.6)	0.14
Congenital gastrointestinal tract pathology	8 (30.8)	21 (36.8)	0.77
Congenital genitourinary tract pathology	2 (7.7)	4 (7.0)	1.00
Respiratory disease before taking culture	6 (23.1)	24 (42.1) ^d	0.15
Respiratory distress syndrome	6 (23.1)	20 (35.1)	0.40
Meconium aspiration syndrome	0 (0)	2 (3.5)	1.00
Persistent pulmonary hypertension of the newborn	0 (0)	3 (5.3)	0.55
Onset of IFI, (days) ^a	26.1 (16.4, 39.3)	18.1 (12.3, 27.7)	0.05
Onset of IFI >14 days after birth	22 (84.6)	35 (61.4)	0.06
IFI during 2015-2017 (compared 1989-2014)	15 (57.7)	35 (61.4)	0.94
Apgar score at 5 minutes <8	9 (34.6)	15 (26.3)	0.61
Previous surgery ^c	9 (34.6)	20 (35.1)	1.00
Total parenteral nutrition ^c	15 (57.7)	41 (71.9)	0.30
Invasive mechanical ventilation ^c	23 (88.5)	43 (75.4)	0.28
Ventilator-associated pneumonia	6 (23.1)	6 (10.5)	0.18
Central line use ^c	16 (61.5)	32 (56.1)	0.82
Central line-associated bloodstream infection	3 (11.5)	4 (7.0)	0.67
Septic shock during onset of infection	5 (19.2)	3 (5.3)	0.10
Type of fungal organism			0.22
<i>Candida albicans</i>	16 (61.5)	28 (49.1)	
<i>Candida parapsilosis</i>	6 (23.1)	22 (38.6)	
<i>Candida tropicalis</i>	2 (7.7)	6 (10.5)	
<i>Candida krusei</i>	1 (3.8)	0 (0)	
<i>Candida</i> species	0 (0)	1 (1.8)	
<i>Trichosporon beigeli</i>	1 (3.8)	0 (0)	

Table 1

Risk factor	Non-survival (<i>n</i> = 26), <i>n</i> (%)	Survival (<i>n</i> = 57), <i>n</i> (%)	<i>p</i> -value
Type of specimens			0.85
Blood	13 (50)	31 (54.4)	
Cerebrospinal fluid	1 (3.8)	3 (5.3)	
Urine	11 (42.3)	18 (31.6)	
Peritoneal fluid	1 (3.8)	5 (8.8)	

^amedian (interquartile range), ^bmean \pm SD, ^cwithin 7 days before or on the date of IFI.

^dOne case had a combination of meconium aspiration syndrome and persistent pulmonary hypertension of the newborn IFI; invasive fungal infection.

Table 2

Risks of non-survival in invasive fungal infection by univariable and multivariable analysis.

Risk factors	Non-survival versus survival			
	Univariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> -value	aOR (95% CI)	<i>p</i> -value
Vaginal delivery	2.23 (0.72, 7.87)	0.19	3.21 (0.94, 10.90)	0.06
Onset of IFI >14 days after birth	3.41 (0.97, 15.38)	0.06	3.12 (0.90, 10.75)	0.07
Septic shock during onset of infection	4.20 (0.74, 29.41)	0.10	5.70 (1.08, 30.03)	0.04

aOR (95% CI), adjusted odds ratio (95% confidence interval).

IFI, invasive fungal infection.

(1 day after initiation of antifungal therapy compared with infants whose catheters were removed or replaced promptly) were the risk factors for mortality in the study in South Africa and USA (Benjamin *et al*, 2006; Ballot *et al*, 2013).

This study has some limitations. We lacked data on the incidence density (*ie*, patient-days), long-term follow-up in the survivor group, diagnostic tests (*ie*, serum detection of β -d-glucan and *Candida* PCR), antifungal susceptibility due to inadequate antifungal therapy, and the major extra daily cost due to calculations from crude costs and incomplete details. Since this study was conducted at a single

center, it may not represent other hospitals (external validity), and the study had low power (we did a post hoc analysis for power = 31% of septic shock was the risk of case fatality rates in neonatal IFI). We did not calculate the sample size before study because there was limited data in risk of mortality rate of neonatal IFI.

In conclusion, neonatal IFI has a low incidence but high mortality and daily cost. Septic shock was a risk factor for death in neonatal IFI.

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