

## Candidemia in Preterm Infants in Neonatal Intensive Care Unit at Zagazig University Hospitals

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### ABSTRACT

**Background:** Candidiasis is a leading cause of blood stream infections in neonatal intensive care units (NICUs) and associated with high mortality and morbidity. Preterm infants are more vulnerable to be affected with candida infections.

**Patients and Methods:** The study is cross-sectional analytical study aimed to evaluate the magnitude of candidemia and evaluate risk factors, proper management, and clinical outcome of candidemia in preterms in NICU in Zagazig University Hospital. It included (103) preterms, their gestational ages of 30 to 37 weeks with weights of 1 to 3 kg. They were admitted to (NICU) of Pediatric Department and Obstetric and Gynecology Department. Investigations were conducted at the Department of Clinical Pathology and Microbiology at Zagazig University Hospitals during the period of 6 months from November 2018 to April 2019.

**Results:** 12.6% of the studied group gave positive fungal culture, *Candida albicans* was the commonest type of fungi found (among 61.5% of the candidemia positive group). 30.8% of candidemia group had taken empirical diflucan as a regimen versus 95.6% of the other group had taken it and the difference between groups was highly statistically significant.

**Conclusion:** Preterms are more vulnerable to candida infection. *Candida albicans* is the commonest type and the use of empirical antifungal therapy to preterms at risk reduces the prevalence of candidemia in the NICU.

**Keywords:** Preterm, Candidemia, NICU, Empirical, Antifungals.

### INTRODUCTION

We can find candida normally inside the body causing no harm but if they grow out of control or affect deep organs of the body (brain, kidney or the heart), candidiasis occur <sup>(1)</sup>.

When candida infection occurs in the blood stream it is called candidemia <sup>(2)</sup> which is associated with high mortality and morbidity <sup>(3)</sup> especially in preterms as they are considered immunocompromised with early gestational ages and low birth weight. Under some circumstances as (catheterization, mechanical ventilation (MV), parenteral nutrition, broad spectrum antibiotics and corticosteroids) systemic candidiasis commonly occur <sup>(4)</sup>.

*Candida* pathogenicity involves: adherence, colonization, infection, dissemination <sup>(5)</sup>. Candidemia in neonates could be presented with signs and symptoms that are indistinguishable from bacterial sepsis and newborns who survive frequently have long-term neurological impairment <sup>(6,7,8)</sup>.

Workup and evaluation for fungal infections in preterm infants includes: CBC, blood culture, urine, and cerebrospinal fluid (CSF) cultures, and liver and renal function <sup>(2)</sup>. Fungal PCR in very low birth weight (VLBW) infants has yielded promising results but requires additional study to be used with every infection evaluation <sup>(9)</sup>.

In patients at risk for invasive candidiasis, empirical antifungal therapy with the administration of antifungals prior to the availability of culture is known to improve survival <sup>(2)</sup>. In infants with blood cultures positive for *Candida*, an appropriate dose of antifungals given. If the patient is receiving fluconazole prophylaxis or if *Candida glabrata* is isolated, then an amphotericin product or micafungin should be given <sup>(10)</sup>.

The present study aimed to evaluate the magnitude of candidemia and evaluate risk factors, proper management, and clinical outcome of candidemia in preterms in NICU in Zagazig University Hospital.

### SUBJECTS AND METHODS

The study is cross-sectional analytical study included (103) preterms, their gestational ages of 30 to 37 weeks with weights of 1 to 3 kg. They were admitted to (NICU) of Pediatric Department and Obstetric and Gynecology Department. Investigations were conducted at the Department of Clinical Pathology and Microbiology at Zagazig University Hospitals during the period of 6 months from November 2018 to April 2019.

Ethical approval:



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A written informed consent was taken from parents of each case.

**The study was approved by our Ethical Committee, Zagazig Faculty of Medicine.**

**Inclusion criteria:**

1. All preterm neonates with gestational age 37 weeks or less and had risk factors of candidemia.
2. Obtaining a written informed consent from parents.

**Exclusion criteria:**

1. Diagnosed genetic disease.
2. Severe congenital malformation and metabolic diseases.
3. A missing written consent.
4. Gestational age more than 37 weeks.

**Methods:**

1. Full history taking: Personal history, present history, past history, prenatal history, natal and postnatal history and family history.
2. Full clinical examination: General examination, vital signs, color, measurements of weight, length, head circumference and local examination for all the body.

3. Radiological chest X-ray posteroanterior view to detect cardiomegaly and pneumonia or any other abnormalities.

4. Laboratory assessment of: Complete blood count (CBC), C-reactive protein (CRP), liver and renal function tests.

5. Laboratory assessment of bacterial and fungal blood cultures, antimicrobial sensitivity for candida as it's considered the gold standard method for candidemia diagnosis.

6.

**Statistical analysis**

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square ( $\chi^2$ ) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following: Probability (P-value): P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

**RESULTS**

The basic characteristics of the studied group are shown in table 1.

**Table (1): The basic characteristics of the studied group**

Variables	Studied group (n=103)	
	Mean ±SD (Range)	
Gestational age (weeks)	33.3 ± 1.95 (30 - 37)	
Weight (Kg)	1.95 ± 0.47 (1 - 3)	
	N	%
Sex		
Male	48	46.6
Female	55	53.4
Mode of delivery		
NVD	17	16.5
Obstructed VD	5	4.9
CS	81	78.6
Site of delivery		
Hospital	61	59.2
Private clinic	42	40.8
APGAR score at birth		
Mean ± SD (Range )	6.22 ± 1.1 (4 – 8)	

No statistical significant relations was found between GA, weight, sex, mode of delivery and site of delivery of studied group and occurrence of candidemia among them (Table 2)

**Table (2): Relation between candidemia and basic characteristics of the studied group**

Variables	Candidemia group (n=13) Mean ±SD		Other group (n=90)		t-test	P-value
	N	%	N	%		
Gestational age (weeks)	32.5 ± 1.6		33.4 1.99		1.54	0.122 NS
Weight (Kg)	1.78 ± 0.51		1.98 0.46		1.4	0.151 NS
<b>Sex</b>						
Male	6	46.2	42	46.7	0.001	0.972 NS
Female	7	53.8	48	53.3		
<b>Mode of delivery</b>						
NVD	1	7.7	16	17.8	1.78	0.412 NS
Obstructed VD	0	0.0	69	76.7		
CS	12	92.3	5	5.6		
<b>Site of delivery</b>						
Hospital	9	69.2	52	57.8	0.617	0.432 NS
Private clinic	4	40.8	38	42.2		

NS:P-value>0.05 is not significant

29.1% of studied group were catheterized, 22.3 % of them were on TPN, 20.4 % of them were on MV and 77.7% of them were on prolonged antibiotic intake (Table 3).

**Table (3): Clinical data and risk factors of the studied group**

Variables	Studied group (n=103)	
	N	%
<b>Catheterization (CVC or umbilical) &gt;7 days</b>		
Yes	30	29.1
No	73	70.9
<b>Activity</b>		
Bad	55	53.4
Moderate	40	38.8
Good	8	7.8
<b>Nutrition</b>		
TPN > 7 days	42	40.8
Ryle and parenteral	23	22.3
Ryle	17	16.5
Oral	8	7.8
MV > 7 days	21	20.4
PROLONGED ANTIBIOTIC INTAKE > 7days	80	77.7
Long hospital stay (7-30 days) (Mean=18.5 days)	80	77.7

Catheterization and mechanical ventilation increased candidemia with high statistical significance (Table 4).

**Table (4): Relation between candidemia and clinical data of the studied group**

Variables	Candidemia group (n=13)		Other group (n=90)		t-test	P value
	Mean ±SD					
APGAR score at birth	5.7 ± 1.03		6.3 ± 1.1		1.85	0.067 NS
	N	%	N	%	X <sup>2</sup>	P
<b>Catheterization &gt;7 days</b>						
Yes	13	100	17	18.9	36.2	<0.001 HS
No	0	0.0	73	81.1		
<b>Activity</b>						
Bad	0	0.0	8	8.9	3.65	0.161 NS
Moderate	3	23.1	37	41.1		
Good	10	76.9	45	50		
<b>Nutrition</b>						
Ryle and parenteral	1	7.7	22	24.4	4.14	0.247 NS
Ryle	2	15.4	15	16.7		
TPN >7 days	10	76.9	45	50		
Oral	0	0.0	8	8.9		
<b>Fate</b>						
Improved	7	53.8	59	65.6	0.706	0.703 NS
Complicated	5	38.5	25	27.8		
Died	1	7.7	6	6.7		
MV >7 days	9	69.2	12	13.3	35.8	<0.001 HS
Prolonged antibiotic intake >7 days	13	100	67	74	4.3	0.253 NS
Long Hospital stay (7-30 days) (Mean=18.5 days)	13	100	67	74	4.3	0.253 NS

**HS: P-value < 0.001 is high significant NS: P-value > 0.05 is not significant**

55.3% of the studied group gave positive bacterial culture results, the commonest type of bacteria found was serratia marcescens (28.1%) (Table 5).

**Table (5): Results of blood culture among the studied group**

Variables	Studied group (n=103)	
	N	%
<b>Bacterial culture</b>		
+ve	57	55.3
-ve	46	44.7
<b>Common bacterial types</b>		
<b>Bacteria positive group (n= 57)</b>		
	N	%
Serratia marcescens	16	28.1
Staph haemolyticus	12	21.1
Pseudomonas aeruginosa	12	21.1
Klebsiella pneumonia	9	15.8
Staph epidermidis	7	12.3
Staph hominis	1	1.8
<b>Fungal culture</b>		
+ve	13	12.6
-ve	90	87.4
<b>Candidemia positive group (n=13)</b>		
<b>Fungal types</b>		
	N	%
Candida albicans	8	61.5
Candida glabrata	2	15.4
Candida tropicalis	3	23.1

The use of empirical diflucan decreased the incidence of candidemia (Table 6).

**Table (6): Relation between candidemia and empirical antifungal drugs (Diflucan) among studied group**

Variables	Candidemia group (n=13)		Other group (n=90)		X <sup>2</sup>	P
	N	%	N	%		
Take empirical diflucan > 7 days	4	30.8	86	95.6	43.2	<0.001 HS
Not taking empirical diflucan	9	69.2	4	4.4		

Isolated candida species were highly sensitive to large number of antifungal drugs (Table 7).

**Table (7): The difference between candida species regarding sensitivity to antifungal drug**

Variables	Candida albicans (n=8)		Candida glabrata (n=2)		Candida tropicalis (n=3)	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Fluconazole	6 (75%)	2 (25%)	2(100%)	0	3(100%)	0
Flucytosine	7(88%)	1(12.5%)	2(100%)	0	3(100%)	0
Voriconazole	8(100%)	0	2(100%)	0	3(100%)	0
Amphotericin B	7(88%)	1(12.5%)	2(100%)	0	3(100%)	0
Caspofungin	8(100%)	0	2(100%)	0	3(100%)	0
Micafungin	8(100%)	0	2(100%)	0	3(100%)	0

## DISCUSSION

Mean gestational age of our studied group was 33.3 ± 1.95 weeks; ranged from 30 weeks up to 37 weeks. This agreed with Hassan study <sup>(11)</sup> who reported that the mean gestational age was 34 weeks. The weights ranged from 1 kg up to 3 kg with mean of 1.95 kg, this agreed with Hassan study <sup>(11)</sup> who reported that the mean birth weight was 2.25 kg. Out of 13 in candidemia positive group: 7 (53.8 %) were females and 6 (46.2%) were males. The male to female ratio was {1:1.165}. This also agreed with Hassan study <sup>(11)</sup> who reported that Out of 214 neonates with positive blood cultures, 139 (65%) patients were females. The male to female ratio was {1:1.8}.

We found no statistical significant relation between gestational age and occurrence of candidemia among the studied group. The mean of gestational age in candidemia positive group was 32.5± 1.6 and 33.4 ± 1.99 in candidemia negative group. Also, there was no statistical significant relation between the weight (kg) and occurrence of candidemia, as the mean of weight in candidemia positive group was 1.78 ± 0.51 and 1.98 ± 0.46 in the other group (candidemia negative group). Also no statistical significant relations between: sex, mode of delivery and the site of delivery of studied group and occurrence of candidemia among them. There were also no statistical significant relations between maternal risks and illness (premature rupture of membranes (PROM), vaginal bleeding, preeclampsia, diabetes mellitus (DM), anemia, urinary tract infection (UTI), polyhydramnios, oligohydramnios) among studied group and occurrence of candidemia. This coped with Fu study <sup>(12)</sup> who reported that: the persistent candidemia cases had a significantly lower birth weight

with P-value less than 0.001 in comparison to non-persistent candidemia group.

We reported that 29.1% of studied group were catheterized, 22.3% of them were on total parenteral nutrition (TPN), 20.4 % of them were on MV, 77.7% of them were on prolonged antibiotic intake more than 7 days and 77.7% of them were long standing in hospital (7-30 days, Mean=18.5 days). This agreed with Wadile and Bhate study <sup>(13)</sup> who reported that the use of multiple invasive devices, such as catheters and endotracheal tubes may be responsible for the nosocomial spread of pathogens through the hands of health care worker (HCW). The hands of HCW and environmental surfaces are newly-appreciated potential reservoirs for nosocomial strains of Candida.

We reported a high statistical significant difference among candidemia patients and other group as regard catheterization (CVC or umbilical) as 100% of candidemia patients were catheterized more than 7 days versus 18.9% only of other group. But other clinical data of the studied group (like type of nutrition, APGAR score, prolonged antibiotic intake more than 7 days) had no statistical significant difference among both groups. In Chen study <sup>(14)</sup> central venous catheterization and TPN were predisposing factors for candidemia. And Yadav study <sup>(15)</sup> stated that prolonged antibiotic use and prematurity were significant risk factors.

Our study shows that 55.3% of the studied group gave positive bacterial culture results, the commonest type of bacteria found was serratia marcescens (28.1%). This agreed with Tsai study <sup>(16)</sup> who reported that gram-negative organisms constituted nearly three-fifth (59.8%) of the case group organisms, which was a significantly

higher percentage than gram-positive organisms (59.8% vs. 39.1%).

In our study only 12.6% of the studied group gave positive fungal culture, and the commonest type of fungi found on assessment was *Candida (C.) albicans* among 61.5% of the candidemia positive group, then 23.1% were positive for *Candida tropicalis*, then among 15.4 % of them were positive for *Candida glabrata*. Hassan study <sup>(11)</sup> reported that eighty-nine isolates from 214 neonates were positive for *Candida spp.* *C. albicans* was the leading causative organism isolated in 55% of all cases diagnosed (n = 49 isolates), 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). Also Jain study <sup>(17)</sup> reported that *C. albicans* was the most common *Candida spp.* (37.6%).

Our study also reported that 30.8% of candidemia group had taken empirical diflucan as a regimen versus 95.6% of the other group, which had taken it and the difference between groups was highly statistically significant as empirical diflucan decreased the incidence of candidemia. This agreed with Greenberg study <sup>(18)</sup> who reported that A total of 136 infants developed invasive candidiasis. The incidence of death or NDI was lower in infants who received empiric antifungal therapy (19 of 38; 50%) compared with those who had not (55 of 86; 64%; OR, 0.27; 95% CI, 0.08-0.86). We reported that *Candida albicans* was 75% sensitive to fluconazole, 88% sensitive to flucytosine, 100% sensitive to voriconazole, 88% sensitive to amphotericin B, 100% sensitive to caspofungin and 100% sensitive to micafungin. *Candida glabrata* was 100% sensitive to all antifungal agents (fluconazole, flucytosine, voriconazole, amphotericin B, caspofungin, micafungin). *Candida tropicalis* was 100% sensitive to all antifungal agents (fluconazole, flucytosine, voriconazole, amphotericin B, caspofungin, micafungin). So, antifungal treatment would be effective and safe in our neonates. This agreed with Hassan study <sup>(11)</sup> who reported that antifungal treatment was effective and safe in neonates. Sixty percent of their cases received antifungal therapy without any significant adverse effects.

## CONCLUSION

Preterms are more vulnerable to candida infection, candida albicans is the commonest type. All species were highly sensitive to antifungal agents and the use of empirical antifungal therapy to preterms at risk reduces the prevalence of candidemia in the NICU.

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