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Candidemia in the Neonatal Intensive Care Unit: Insights on Epidemiology and Antifungal Drug Susceptibility Patterns

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Abstract

Background: Being the culprit in 9% - 13% of neonatal bloodstream infections (BSIs), candidemia has been escalating to worrisome levels in the past few decades. While *C. albicans* has traditionally been the most common isolate, non-*albicans Candida* spp. are currently gaining a foothold.

Objectives: We endeavored to investigate the epidemiological features of neonatal candidemia with special emphasis on non-*albicans* candidemia. Hence, we evaluated the incidence, risk factors, antifungal susceptibility, and case fatality rate of candidemia patients in the NICU.

Methods: Blood samples were collected from 1296 neonates admitted to the NICU of a tertiary care hospital. Then, only neonates with positive blood cultures were enrolled. Incidence and risk factors of *albicans* and non-*albicans* candidemia were evaluated. The E-test was employed to determine the minimum inhibitory concentrations of fluconazole, itraconazole, voriconazole, amphotericin B, and caspofungin.

Results: Out of 214 neonates with BSI, candidemia afflicted 32 neonates (15%). The predominant isolate was *C. tropicalis* (43.8%), followed by *C. albicans* (25%). Both antibiotic use and antifungal prophylaxis were contributing factors (P values of 0.02 and < 0.01, respectively). Susceptibility testing revealed that 87.5% of the retrieved *Candida* isolates were sensitive to amphotericin B, 81.25% to fluconazole, 75% to voriconazole, and 62.5% to itraconazole while 48.75% were sensitive to caspofungin.

Conclusions: Neonatal candidemia often carries an ominous prognosis. The worldwide progressive shift towards non-*albicans* candidemia necessitates regular surveillance and monitoring of laboratory data. An epidemiological knowledge is critical in terms of preemptive management that should encompass disciplined infection control practices and a restrictive policy for antibiotic and antifungal prophylaxis.

Keywords: *Candidemia*, *C. tropicalis*, Neonates, NICU, Non-*albicans Candida*

1. Background

Ranking as the fourth most common cause of nosocomial bloodstream infections (BSIs) (1), candidemia has been surging as a daunting challenge to both clinicians and infection control practitioners. In the neonatal intensive care unit (NICU), candidemia has been the third most common cause of late-onset sepsis, accounting for 9% - 13% of the neonatal BSIs (2).

Because of their immature immune system, neonates are particularly vulnerable to invasive candidemia. Incriminated factors include prolonged endotracheal intubation, total parenteral nutrition (TPN), indwelling venous catheterization, and broad-spectrum antibiotics (3). While *Candida albicans* has long been accountable for the majority of candidemia cases, non-*albicans Candida* spp. (NAC) are now soaring on a global scale (4).

Early initiation of antifungal therapy would have a huge impact on the disease prognosis. However, due to the lack of specific signs and symptoms, clinching a definite diagnosis of candidemia is a tedious process. This, in turn, has led to a substantial surge in morbidity, mortality, and health-care expenditures (5).

2. Objectives

In this study, we aimed to evaluate the risk factors predisposing to neonatal candidemia with special emphasis on non-*albicans* candidemia. Hence, we endeavored to investigate the incidence, risk factors, antifungal susceptibil-

ity, and the case fatality rate of candidemia patients in the NICU of a tertiary care hospital.

3. Methods

3.1. Ethical Consideration

Before commencement of the study, the protocol was approved by the Ethics Committee of the Pediatrics and Neonatology Department, Cairo University, Cairo, Egypt.

3.2. Study Population

This cross-sectional analytical study was conducted from October 2015 throughout October 2017 in the Departments of Pediatrics and Neonatology, Clinical Pathology, and Microbiology at Kasralainy Tertiary Care Hospital, Cairo, Egypt. Out of 1296 neonates admitted to the NICU at Al-Mounira Pediatric University Hospital with a clinical suspicion of septicemia, 214 neonates had positive blood culture results and were included in this study. Prior to enrollment, informed consents were obtained from the parents or guardians. All participating neonates were subjected to history taking and clinical examination.

The following data were gathered: Admission age; gestational age; mode of delivery; premature rupture of membranes (PROM); gender; birth weight; underlying maternal illness; hypoglycemia; hyperglycemia; metabolic acidosis; seizures; poor feeding; skin rash; hepatomegaly; invasive and non-invasive ventilation; pneumonia; TPN; necrotizing enterocolitis (NEC); intracranial hemorrhage (ICH); central venous catheterization; chest intubation; steroid administration; bronchopulmonary dysplasia (BPD); duration of hospitalization; use of H_2 blockers; use of carbapenems, vancomycin, fluoroquinolones, and other antibiotics; antifungal drug prophylaxis; and the outcome of candidemia.

3.3. Microbiological Methods

From each of the 1296 neonates, two blood samples were collected into pediatric Bactec blood culture bottles (BD Diagnostic Systems). The bottles were transported to the laboratory and immediately incubated in the blood culture systems (BD BACTEC™ 9050). Any growth was subcultured onto 5% sheep blood agar, MacConkey's agar, and Sabouraud's dextrose agar (SDA) with chloramphenicol (0.05%) (Oxoid Co. England) and then incubated at 37°C. The diagnosis of candidemia was settled by the presence of at least one positive blood culture showing pure growth of *Candida* spp. together with supportive clinical findings (6). The isolated *Candida* spp. were identified by colony morphology on SDA, germ tube test (7), and chromogenic media (CHROMagar™ *Candida*).

The minimum inhibitory concentrations (MICs) of fluconazole (FLU), itraconazole (ITR), voriconazole (VOR), amphotericin B (AMB), and caspofungin (CSP) were determined using the E-test (bioMérieux-SA, France). The guidelines for the *in vitro* susceptibility of *Candida* spp. to FLU, ITR, and VOR were adopted from the M27-A3 document of the Clinical and Laboratory Standards Institute (8), while literature guidelines for AMB were adopted from Sanita et al. (9) and Negri et al. (10). The MIC results for CSP were interpreted using revised clinical breakpoints for echinocandins (11, 12). Quality control strains (*Candida albicans* ATCC® 10231, *C. albicans* ATCC 90028, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258) were supplied by Microbiologics 200 Cooper Avenue North, St. Cloud, MN 56303, United States.

3.4. Statistical Analysis

Data management and statistical analysis were performed using the statistical package for social sciences (SPSS) version 21. Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Comparisons between groups with respect to normally distributed numeric variables were made using the *t*-test. Non-normally distributed numeric variables were compared by the Mann-Whitney test. For categorical variables, differences were analyzed with the Chi-square test and Fisher's exact test. Comparisons between the different prognostic factors were made using the Logrank test. All significant variables were entered into the Cox Proportional Hazards Model to detect the most important factors that independently affected the outcome. All P values were two-sided. A P value < 0.05 was considered significant.

4. Results

Out of 214 neonates with positive blood cultures, 139 (65%) patients were females. The male to female ratio was 1:1.8.

Upon cultivation, pure *Candida* growth was retrieved from 32/214 cases (15%) while 182/214 (85%) neonates had a bacterial BSI. In the candidemia group, *C. albicans* was isolated from only 25% of the cases while NAC spp. were responsible for 75% of the cases, with *C. tropicalis* being the most frequently retrieved isolate (43.8%). Meanwhile, *C. krusei* was isolated from 6.2% of the cases and other *Candida* spp. from 25% of the cases.

The MICs of AMB, ITR, FLU, and VOR, as well as CSP, were determined using the E-test (Table 1).

In the candidemia group, the mean gestational age was 34 weeks while the mean birth weight was 2.25 kg. The demographics of *albicans* candidemia patients are compared with those of NAC patients in Table 2. Of note, a statistically significant difference was found between the

Table 1. Antifungal Drug Susceptibility Results as Revealed by the E-test

Drug	MIC range, μg/mL	Sensitive[a]	Intermediate[a]	Resistant[a]
AMB	0.023 - 32	28 (87.5)	-	4 (12.5)
ITR	0.016 - 32	20 (62.5)	2 (6.25)	10 (10.25)
FLU	0.25 - 256	26 (81.25)	2 (6.25)	4 (12.5)
VOR	0.016 - 32	24 (75)	2 (6.25)	6 (18.75)
CSP	0.003 - 32	22 (68.75)	4 (12.5)	6 (18.75)

Abbreviations: AMB, amphotericin B; CSP, caspofungin; FLU, fluconazole; ITR, itraconazole; MIC, minimum inhibitory concentration; VOR, voriconazole.
[a]Values are expressed as No. (%).

two groups concerning the age at admission, as well as the birth weight.

In the meantime, the potential predisposing factors and clinical characteristics were compared between the candidemia and bacteremia groups (Table 3). Risk factors incriminated in candidemia were antifungal (FLU) prophylaxis and antibiotic use (fluoroquinolones).

On the other hand, NAC was more likely to develop in neonates subjected to invasive ventilation, as well as neonates with prolonged venous catheterization (Table 4).

In the candidemia group, the case fatality rate was 56.2%, which was quite close to that of the bacteremia group (56%). Meanwhile, the case fatality rate was slightly higher in NAC (58.3%, 14/24) than in *albicans* candidemia (50%).

5. Discussion

Candida spp. have been emerging as leading pathogens in neonatal BSIs, pertaining to substantial morbidity and mortality (13). Therefore, it is crucial for both physicians and microbiologists to promote the prevention, early detection, and prudent management of candidemia in high-risk neonates.

In this study, 65% of the patients were females, with a male to female ratio of 1:1.8. Consistent with our finding, Juyal et al. (6) reported that 60.4% of their patients were females, with a male to female ratio of 1:1.5.

In this study, candidemia accounted for 15% of the neonatal BSIs cases. Corroborating our finding, Jain et al. (14) reported that candidemia accounted for 15.8% of the neonatal BSIs. Nonetheless, a higher incidence of 20.4% was reported by Rao et al. (15).

Out of the 32 retrieved *Candida* isolates, 75% were NAC. In line with our result, Juyal et al. (16) reported NAC as responsible for 80.6% of neonatal candidemia.

Meanwhile, *C. tropicalis* was the most commonly encountered *Candida* spp. (43.8%), followed by *C. albicans* (25%). This was in accordance with Yadav et al. (17) who stated that *C. tropicalis* was the most frequent *Candida* spp. (26.9%), followed by *C. albicans* (11.5%). On the other hand, Jain et al. (14) reported that *C. albicans* was the most common *Candida* spp. (37.6%).

Among the 32 *Candida* isolates, 87.5% were susceptible to AMB, 62.5% to ITR, 81.25% to FLU, 75% to VOR, and 68.75% to CSP. That was lower than the results of earlier studies (4, 17), which revealed that 100% of *Candida* isolates were sensitive to FLU, VOR, ITR, and AMB.

Notably, numerous risk factors including broad-spectrum antibiotics have been reported as predisposing factors for candidemia (18). The widespread use of antimicrobial agents can suppress the bacterial microbiota, paving the way for the dominance of *Candida* colonization (19). In this study, fluoroquinolone empiric use and fluconazole prophylaxis proved to be significant risk factors; however, none of the other potential risk factors proved significant.

In an earlier study (3), central venous catheterization and TPN were predisposing factors for candidemia. On the other hand, Yadav et al. (17) stated that prolonged antibiotic use, very low birth weight, and prematurity were significant risk factors. This myriad of the findings is attributable in part to variations in host factors and infection control practices, and they notably reflect the epidemiological shift of *Candida* spp. (20).

In the meantime, factors contributing to the development of NAC were low birth weight, the age at admission, invasive ventilation, and the duration of central venous catheterization. In accordance with that, Garzillo et al. (21) stated that NAC was linked to birth weight, gestational age, and the duration of central venous catheterization, but not to the length of hospital stay. These results were in line with those of Juyal et al. (6) who reported low birth weight and indwelling catheters as contributory factors to NAC; yet, they added broad-spectrum antibiotics as a risk factor.

Indeed, several studies (7, 16) have drawn attention to the tendency of *Candida* spp. to adhere to foreign materials. Some studies have proven that non-*albicans Candida* have even a higher capability of such adherence (22). Once they adhere to fibrinogen or platelets on a venous catheter, they can form a biofilm. On the one hand, this biofilm protects the fungus against immune responses and antifungal agents and on the other hand, it acts as a reservoir for sys-

Table 2. Demographics of the Enrolled Neonates[a]

Variables	Bacteremia Group	Candidemia Group	P Value	*Albicans* Candidemia Subgroup	NAC Subgroup	P Value
Age at admission, d	4 (1 - 14)	4 (1 - 14)	0.717	7 (1 - 14)	3 (1 - 12)	0.021
Length of hospital stay	36 (2 - 88)	40 (2 - 88)	0.347	32 (6 - 82)	43 (2 - 88)	0.383
Gestational age, wk	34 ± 4	34 ± 3	0.370	37 (36 - 38)	35 (27 - 38)	0.063
Birth weight, kg	2.11 ± 0.82	2.25 ± 0.9	0.397	2.85 (1.9 - 3.7)	1.93 (0.9 - 3.9)	0.023
Male gender	62 (82.7)	13 (17.3)	0.473	4 (30.8)	9 (69.2)	0.684

[a]Values are expressed as median (range), mean ± SD and No. (%).

Table 3. Potential Risk Factors in Neonates with Candidemia Compared to Those with Bacterial BSI[a]

Variables	Candidemia Group	Bacteremia Group	P Value
Mode of delivery			
NVD	18 (15.9)	95 (84.1)	0.672
CS	14 (13.9)	87 (86.1)	
PROM	6 (11.8)	45 (88.2)	0.464
Maternal illness	16 (15.0)	91 (85.0)	1.0
Signs of sepsis			
RD	22 (14.9)	126 (85.1)	0.957
Hypotension	26 (14.9)	148 (85.1)	0.993
Poor capillary perfusion	26 (14.9)	148 (85.1)	0.993
Edema	8 (14.3)	48 (85.7)	0.870
Hypoglycemia	14 (15.1)	79 (84.9)	0.971
Hyperglycemia	22 (15.1)	124 (84.9)	0.945
Metabolic acidosis	26 (14.9)	148 (85.1)	0.993
Seizures	10 (15.2)	56 (84.8)	0.957
Poor feeding	22 (14.9)	26 (85.1)	0.957
Hepatomegaly	8 (14.5)	47 (85.5)	0.922
Jaundice	18 (15.1)	101 (84.9)	0.937
Pneumonia	26 (15.3)	144 (84.7)	0.783
Invasive ventilation	24 (14.9)	137 (85.1)	0.947
TPN	23 (17.3)	110 (82.7)	0.219
Intercostal tube insertion	18 (15.3)	100 (84.7)	0.942
NEC	18 (14.9)	103 (85.1)	0.971
ICH	12 (17.6)	56 (82.4)	0.451
BPD	14 (15.1)	79 (84.9)	0.971
Antenatal steroids	14 (14.9)	80 (85.1)	0.983
Antimicrobial therapy before culture results			
Aminoglycoside use	2 (20)	8 (80)	0.647
Amikacin use	14 (14.6)	82 (85.4)	0.891
Fluoroquinolone use	15 (10.8)	124 (89.2)	0.020
Carbapenem use	26 (14.9)	148 (85)	0.993
Vancomycin use	26 (14.8)	150 (85.2)	0.873
Fluconazole prophylaxis	24 (55.8)	19 (44.2)	<0.001
Central venous line	20 (15.0)	113 (85)	0.965
Central venous line duration, median (range)	10 (5 - 32)	10 (5 - 32)	0.944

Abbreviations: BPD, bronchopulmonary dysplasia; CS, cesarean section; ICH, intracranial hemorrhage; NEC, necrotizing enterocolitis; NVD, normal vaginal delivery; PROM, premature rupture of membranes; RD, respiratory distress; TPN, total parenteral nutrition.
[a]Values are expressed as No. (%) unless otherwise indicated.

temic spread (19).

The case fatality rate in the candidemia group was 56.2%, while in the bacteremia group, it was 56%. This was close to the fatality rate of 54% reported by Hammoud et al. (23). Meanwhile, the case fatality rate in the *albicans* candidemia group was 50%, while in the NAC group, it was

Table 4. Risk Factors and Clinical Characteristics of *albicans* Candidemia Compared to NAC[a]

Variables	*Albicans* Candidemia	NAC	P Value
Mode of delivery			
NVD	2 (11.1)	16 (88.9)	0.096
CS	6 (42.9)	8 (57.1)	
PROM	0 (0)	6 (100)	0.296
Maternal illness	4 (25)	12 (75)	1
Signs of sepsis			
RD	4 (18.2)	18 (81.8)	0.186
Hypotension	4 (15.4)	22 (84.6)	0.023
Poor capillary perfusion	6 (23.1)	20 (76.9)	0.625
Edema	0 (0)	8 (100)	0.059
Hypoglycemia	4 (28.6)	10 (71.4)	0.073
Hyperglycemia	6 (27.3)	6 (72.7)	0.66
Metabolic acidosis	6 (23.1)	20 (76.9)	0.625
Seizures	2 (20)	8 (80)	0.66
Poor feeding	4 (18.2)	18 (81.8)	0.186
Hepatomegaly	0 (0)	8 (100)	0.056
Jaundice	4 (22.2)	14 (77.8)	0.703
Pneumonia	4 (15.4)	22 (84.6)	0.023
Invasive ventilation	4 (16.7)	20 (83.3)	0.059
TPN	6 (26.1)	17 (73.9)	0.82
Intercostal tube insertion	4 (22.2)	14 (77.8)	0.703
NEC	2 (11.1)	16 (88.9)	0.96
ICH	0 (0)	12 (100)	0.011
BPD	2 (14.3)	12 (85.7)	0.412
ntenatal steroids	2 (14.3)	12 (85.7)	0.412
Antimicrobial therapy before culture results			
Aminoglycoside use	0 (0)	2 (100)	1
Amikacin use	2 (14.3)	12 (85.7)	0.421
Fluoroquinolone use	4 (26.7)	11 (73.3)	1
Carbapenem use	6 (23.1)	20 (76.9)	0.625
Vancomycin use	6 (23.1)	20 (76.9)	0.625
Fluconazole prophylaxis	6 (25)	18 (75)	1
Central venous line	6 (30)	14 (70)	0.399
Central venous line duration, median (range)	7 (5 - 10)	15 (7 - 32)	0.007

Abbreviations: BPD, bronchopulmonary dysplasia; CS, cesarean section; ICH, intracranial hemorrhage; NEC, necrotizing enterocolitis; NVD, normal vaginal delivery; PROM, premature rupture of membranes; RD, respiratory distress; TPN, total parenteral nutrition.
[a]Values are expressed as No. (%) unless otherwise indicated.

58.3%. This was in accordance with the results of Al Thaqafi et al. (24) who reported the mortality rate in *albicans* candidemia as 50% and in NAC as 57.8%.

It has been observed that drug resistance in *Candida* spp. is rare and thus an unlikely cause of treatment failure. This is exemplified by the absence of a clear correlation between susceptibility patterns and patients' outcomes (25). Hence, studies have reiterated the importance of host factors in the failure of antifungal therapy. One of these factors is the immaturity of the neonates' immune system that may render them unable to eliminate a fungus despite that its growth has been inhibited (26). The higher fatality in NAC patients may be attributable to the underlying medical conditions of the neonates (21); however, further studies are warranted to investigate the mortality risk factors.

Worth mentioning, the current study is limited by having a single center design with a relatively small sample size; hence, it might be difficult to generalize the findings to various settings. Nonetheless, the study emphasizes the need for vigilant surveillance and monitoring of neonates admitted to the ICU. In order to attain timely and actionable results, judicious antibiotic stewardship and early antifungal treatment should essentially be implemented in

all NICUs.

Footnote

Ethical Considerations: Before commencement of the study, the protocol was approved by the Ethics Committee of the Pediatrics and Neonatology Department, Cairo University, Cairo, Egypt.

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