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# Neonatal Intensive Care Unit Candidemia: Epidemiology, Risk Factors, Outcome, and Critical Review of Published Case Series

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**Abstract** Evaluation of epidemiological trends, risk factors, and clinical outcome associated with candidemia at a neonatal intensive care unit is reported. From January 2005 to December 2009, forty candidemia cases were identified. *C. albicans* and *C. parapsilosis* were the most common species recovered (69 and 24%, respectively). All *C. parapsilosis* strains were susceptible to antifungals, whereas, *C. albicans* exhibited higher resistance rates to azoles. Low birth weight, low gestational age, presence of central lines, endotracheal intubation, total parenteral nutrition, previous use of antibiotics, steroids, previous episode(s) of bacteremia and prolonged stay in intensive care unit were common features associated with candidemia. *C. albicans* was most often isolated from extremely low birth weight neonates as compared to non-*albicans Candida* ($P < 0.01$). Mortality rate was 35.7% and was associated with low gestational age ($P < 0.01$), low birth weight ($P < 0.01$), and presence of renal failure ($P < 0.05$). Furthermore, a critical review of recent published case series is presented.

**Keywords** Neonates · Candidemia · Antifungals · Birth weight · Prematurity · Mortality

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## Introduction

Bloodstream infections are major causes of morbidity and mortality and represent the eighth leading cause of infant death [1]. Candidemia is the second most common nosocomial bloodstream infection in very low weight neonates and children [2, 3]. Mortality rates associated with candidemia remain significant, despite use of advanced therapeutic approaches [3]. Although most data collected are from adults, available evidence indicates that *Candida* species cause a high proportion of bloodstream infections among children, especially neonates [4]. Neonatal candidemia frequently complicates clinical course of preterm neonates, especially those with underlying disease [5], whereas, central nervous system involvement and neurologic impairment is common. Central venous catheters and arterial lines, parenteral nutrition, mechanical ventilation and extended use of antimicrobials enhance the risk of neonatal candidemia [6]. The aim of this study was to investigate the prevalence of candidemia and etiological agents, predisposing

factors and outcome among neonates, during a 5-year period. Furthermore, a review of recent published case series is presented.

## Materials and Methods

A retrospective cohort study of bloodstream infections caused by *Candida* species was carried out in Neonatal Intensive Care Unit (NICU) at the University General hospital of Patras, a level III referral unit, located in southwestern Greece. The study took place over a 5-year period (2005–2009). NICU consists of 20 beds with about 350 admissions per year. All candidemia cases were evaluated in terms of mycological data including species isolation and antifungal susceptibility, as well as, patient data including demographic data, risk factors, and outcome. *Candida* isolation from blood cultures was performed by BacT/Alert 3D (Biomerieux SA, Marcy l'Etoile, France). All isolates were identified using the germ tubes test and API 20C AUX system (Biomerieux SA, Marcy l'Etoile, France). Antifungal susceptibility was carried out by *E* test (AB Biodisk) on RPMI–2% glucose agar and MICs for amphotericin B, 5-flucytosine, ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole, and caspofungin were evaluated according to the manufacturer's instructions, as previously described [7]. Resistance to 5-flucytosine was defined as MIC $\geq$32 mg/L, to fluconazole $\geq$64 mg/L, to itraconazole $\geq$1 mg/L, to voriconazole $\geq$4 mg/L. MIC cutoff value for susceptibility to caspofungin and amphotericin B was 2 and 1 mg/L, respectively [8–10]. Isolates demonstrating MIC $\leq$1 mg/L were considered susceptible to posaconazole [8, 11], while strains with MIC $\geq$1 mg/L were interpretive as resistant to ketoconazole.

All infants nursed were included in the study. A candidemia case was defined as a positive blood culture with a *Candida* spp in an eligible subject during the study period [12]. Persistent *Candida* bloodstream infection has been defined in various studies as candidemia with duration greater than 2–5 days in spite of adequate dosing of conventional antifungals [13]. Infants with birth weight less than 2,500 g were defined as low birth weight, less than 1,500 g of very low birth weight and less than 1,000 g were considered as extremely low birth weight infants (ELBW) [13]. Prematurity was defined as gestational age of less than 37 weeks [14]. Other risk factors included presence of central venous catheters, endotracheal intubation, total parenteral nutrition, previous use of antibiotics, steroids, duration of stay in NICU, previous bacteremia, respiratory disorders, jaundice, liver and renal deficiency, central nervous system disorders, congenital malformations involving heart and large vessels, congenital malformations involving the alimentary tract, complications involving the intestinal tract (bowel perforation, necrotizing enterocolitis). Statistical analysis was performed using SPSS for Windows v.17.0.1 [15]. Differences in proportions were evaluated using the Chi-square test. Statistical significance was defined as $P < 0.05$.

## Results

### Mycological Data

During the study period, forty candidemia cases were treated in NICU. The species identified were in twenty-seven cases *C. albicans* (67.5%), in ten cases *C. parapsilosis* (25%), in two cases *C. tropicalis*, and in one case *C. glabrata*. A decreasing pattern in candidemia incidence was observed during the study period, from eleven cases in 2005 and twelve in 2006 to seven cases (2007), and five cases during the last 2 years of the survey. In two patients, *Candida* was isolated from cerebrospinal fluid, and in four cases, echocardiograms were consistent with endocarditis [16]. No cases of *Candida* endophthalmitis/retinitis, isolation of *Candida* spp from a sterile cavity, lungs or other organs was observed. However, *Candida* was also isolated from urine in five candidemia cases.

All *C. parapsilosis* and *C. tropicalis* strains were susceptible to amphotericin B, 5-flucytosine, azoles, and caspofungin (Fig. 1). All *C. albicans* strains were susceptible to amphotericin B and 5-flucytosine, and only one strain was resistant to caspofungin (susceptibility rate 96.5%). In terms of susceptibility to azoles, voriconazole seems to be the most efficient (93%), whereas, susceptibilities to fluconazole, itraconazole, ketoconazole, and posaconazole were 89, 81.5, 85, and 87.5%, respectively (Fig. 1).

### Demographic Characteristics and Risk Factors

Thirty-four candidemia cases (85%) occurred at low birth weight neonates, and thirty-three cases (82.5%)

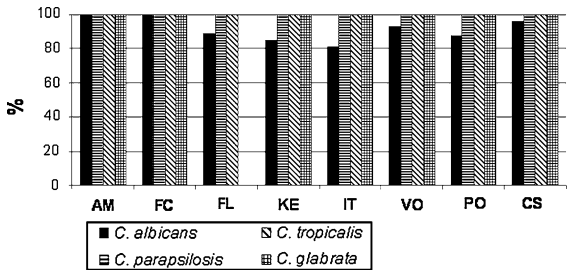


**Fig. 1** Antifungal susceptibility rates. *AM* amphotericin B, *FC* 5-flucytosine, *FL* fluconazole, *KE* ketoconazole, *IT* itraconazole, *VO* voriconazole, *PO* posaconazole, *CS* caspofungin

at low gestational age neonates. Previous use of antibiotics and steroids was reported in 36 cases (90%). Invasive procedures were common at NICU patients, such as use of central indwelling catheters (75%), endotracheal intubation (80%), and total parenteral nutrition (95%). All neonates with candidemia had at least one episode of bacteremia before its occurrence. Gastrointestinal pathology such as necrotizing enterocolitis was identified in 12.5% of candidemia patients. Respiratory disorders were observed in 19 neonates with candidemia (47.5%), jaundice in 10 (25%), CNS disorders in 4 (10%), heart and vessels malformations in 6 (15%), and alimentary tract malformations in 3 (7.5%) neonates. Liver and renal failure was observed also in 3 neonates (7.5%).

## Evaluation of Isolated *Candida* spp and Specific Risk Factors

Isolation of *C. albicans* or non-*albicans Candida* and presence of specific risk factors was evaluated. Statistical data revealed that low birth weight is associated with candidemia due to *C. albicans* ($P < 0.05$). *C. albicans* was isolated at a higher rate, eleven among twelve candidemia cases involving ELWB ($P < 0.01$). No statistically significant differences were observed between *C. albicans* and *Candida* non-*albicans* candidemia regarding presence of other risk factors (Table 1).

## Outcome

Despite appropriate diagnosis and treatment, fifteen neonates with candidemia died (35.7%,). Fourteen had low birth weight (less than 2,500 g), eleven less than 1,500 g, and nine less than 1,000 g. Low birth weight and low gestational age were associated with poor outcome ($P < 0.01$). Presence of renal failure was also associated with poor outcome ($P < 0.05$). No significant association between outcome and presence of endotracheal intubation, central lines, parenteral alimentation or other risk factors was found ($P > 0.05$) (Table 2). In addition, no statistically significant differences in survival rates between neonates with candidemia caused by *C. albicans* (63%) and neonates

**Table 1** Risk factors for neonatal candidemia

| | *Candida* spp $N = 40$ *N* (%) | *C. albicans* $N = 27$ *N* (%) | NAC $N = 13$ *N* (%) | *P* |
|---|---|---|---|---|
| Low birth weight <2,500 g | 34 (85) | 22 (81.5) | 12 (92.3) | <0.05 |
| ELBW <1,000 g | 12 (30) | 11 (41) | 1 (7.7) | <0.01 |
| Low gestational age <37 w | 33 (82.5) | 22 (81.5) | 11 (84.6) | NS |
| Central lines | 30 (75) | 20 (74) | 10 (77) | NS |
| Endotracheal tubes | 32 (80) | 22 (81.5) | 10 (77) | NS |
| TPN | 38 (95) | 26 (96) | 12 (92.3) | NS |
| Use of antibiotics or steroids | 36 (90) | 24 (89) | 12 (92.3) | NS |
| One episode of bacteremia at least | 40 (100) | 27 (100) | 13 (100) | NS |
| Respiratory disorders | 19 (47.5) | 11 (41) | 8 (61.5) | NS |
| CNS disorders | 4 (10) | 1 (3.7) | 3 (23) | NS |
| Congenital malformations | 9 (22.5) | 5 (18.5) | 4 (31) | NS |
| Complications of intestinal tract | 6 (15) | 4 (15) | 2 (15) | NS |
| Stay in ICU (>14 days) | 38 (95) | 25 (92.5) | 13 (100) | NS |

*NAC Candida* non-*albicans*, *NS* no statistically significant difference, *ELBW* extremely low birth weight, *TPN* total parenteral nutrition, *CNS* central nervous system, *ICU* intensive care unit

**Table 2** Risk factors and neonatal outcome

| | Survived $N = 25$ $N$ (%) | Died $N = 15$ $N$ (%) | $P$ |
|---|---|---|---|
| Low birth weight | 20 (80) | 14 (93.3) | <0.01 |
| Low gestational age | 18 (72) | 13 (87) | <0.01 |
| Central lines | 17 (68) | 13 (87) | NS |
| Endotracheal tubes | 18 (72) | 14 (93) | NS |
| TPN | 23 (92) | 15 (100) | NS |
| Use of antibiotics and/or steroids | 23 (92) | 13 (87) | NS |
| One episode of bacteremia at least | 25 (100) | 15 (100) | NS |
| Respiratory disorders | 13 (52) | 8 (53) | NS |
| CNS disorders | 2 (8) | 2 (13.3) | NS |
| Congenital malformations | 7 (28) | 1 (6.7) | NS |
| Complications of intestinal tract | 2 (8) | 4 (27) | NS |
| Renal deficiency | 0 (0) | 3 (20) | <0.05 |
| Stay in ICU >14 days | 25 (100) | 14 (93) | NS |
| *C. albicans* | 17 (68) | 10 (67) | NS |
| *C. parapsilosis* | 6 (24) | 4 (27) | NS |
| *C. glabrata* | 0 (0) | 1 (6.7) | NS |
| *C. tropicalis* | 2 (8) | 0 (0) | NS |
| NAC | 8 (32) | 5 (33.3) | NS |

*NS* no statistically significant difference, *TPN* total parenteral nutrition, *CNS* central nervous system, *ICU* intensive care unit, *NAC Candida* non-*albicans*

with candidemia caused by *Candida* non-*albicans* (61.5%) were observed (Table 1). During the study period, the only one candidemia case due to *C. glabrata* involved an ELWB neonate and was fatal, whereas, both two cases due to *C. tropicalis* were efficiently treated.

### Cases of Persistent Candidemia

Thirteen candidemia cases (32.5%) were identified as persistent candidemia (duration more than 7 days–five cases more than 14 days), three of them were complicated with endocarditis, whereas, three (23%) were fatal. Seven persistent candidemia cases (54%) were due to *C. albicans* and six (46%) due to *C. parapsilosis*. Eight neonates with persistent candidemia were less than 1,500 g and ten less than 2,500 g. In three cases, *Candida* spp was isolated from urine.

## Discussion

There are several important observations in this study. Review of published case series on epidemiology, risk factors, and outcome of NICU candidemia is summarized in Table 3. *C albicans* is also the most common blood isolate in our NICU (67.5%) [17–28]. Similarly, *C. parapsilosis* is the second commonest isolate and constitutes one-fourth of blood isolates (25%) [17–22, 25–27]. This finding may be attributed to the use of central catheters [29], parenteral alimentation at premature infants [5], gastrointestinal colonization [5], and transmission through the hands of health care workers [28]. In some areas, mainly Australia, South America/Brazil, Spain, and Portugal, *C. parapsilosis* counts for the majority of candidemia cases [5, 12, 30–34]. *C. glabrata* and *C. tropicalis* are uncommon in neonates (2.5 and 5%, respectively), whereas, less common *Candida* species, such as *C. krusei*, *C. lusitaniae*, and *C. guilliermondii*, are absent.

According to current guidelines, both amphotericin B and fluconazole appear acceptable choices for the therapy of neonatal candidemia [35]. *Candida* isolates from neonatal candidemia are susceptible to most agents [5, 12, 18, 25, 27, 34]. More specifically, amphotericin B has an excellent antifungal activity, whereas, fluconazole is active against all *C. parapsilosis* isolates. It exhibits an antifungal action to 89% of *C. albicans* isolates. Voriconazole seems a very promising agent exhibiting the highest susceptibility rate (93%) among azoles. It has been shown that voriconazole has good distribution into brain, lungs,

**Table 3** Review of published case series

| Reference | Country of origin | Study period | No of cases | *Candida* spp (%) | Susceptibility test (S %) | Risk factors for candidemia | Risk factor for mortality | Mortality (%) | Therapeutic choices |
|---|---|---|---|---|---|---|---|---|---|
| Fridkin et al. [17] | USA | 1995–2004 | 1997 neonates (<1,000 g, $n = 1,472$) | *C. albicans* (57.9), *C. parapsilosis* (33.7), *C. tropicalis* (3.8), *C. lusitaniae* (2.3) *C glabrata* (2) | | Birth weight <1,000 g and 1,000–1,500 g Neonates with *C. parapsilosis* were significantly older vs neonates with *C. albicans* (26 vs 19 days) | | 13 | |
| Saiman et al. [18] | USA | 1993–1995 | 35 neonates (<1,000 g, $n = 23$) | *C. albicans* (62.9), *C. parapsilosis* (28.6) | All susceptible to amphotericin B, 86% of *C. albicans* isolates susceptible to fluconazole | Birth weight, abdominal surgery, gestational age < 32 weeks, 5-min Apgar score < 5, shock, DIC, prior use of intralipids and antibiotics, TPN, CVCs, H2 blockers, intubation, length of stay >7 days, GI colonization | | 22.9 | |
| Benjamin et al. [19] | USA | 1998–2001 | 307 neonates (all <1,000 g) | *C. albicans* (50), *C. parapsilosis* (43) | | Birth weight cephalosporins lack of enteral feeding | Delayed catheter removal (especially *C. parapsilosis vs C. albicans* infection), gestational age <25 weeks | 31.6 | Amphotericin B ± second antifungal agent |
| Shetty et al. [20] | USA | 1998–2000 | 35 neonates | *C. albicans* (54), *C. parapsilosis* (26), *C. glabrata* (14) | | Birth weight, gestational week <26 weeks, vaginal delivery, abdominal surgery | | 20 | |
| Festekjian and Neely [21] | USA | 2000–2006 | 194 children (<1 year, $n = 55$) | *C. albicans* (56), *C. parapsilosis* (25), *C. glabrata* (10), *C. tropicalis* (3), *C. lusitaneae* (3), *C. krusei* (2.6) | | Prematurity, chronic medical conditions, CVC, admission to ICU, receipt of chemotherapy, steroids, immunosuppressive agents, broad-spectrum antibiotic | | 11 | |

**Table 3** continued

| Reference | Country of origin | Study period | No of cases | *Candida* spp (%) | Susceptibility test (S %) | Risk factors for candidemia | Risk factor for mortality | Mortality (%) | Therapeutic choices |
|---|---|---|---|---|---|---|---|---|---|
| Neu et al. [12] | USA | 2002–2006 | 154 children (<3 months, $n = 51$) | *C. parapsilosis* (43) *C. albicans* (26), *C. glabrata* (12.8) *C. tropicalis* (6.4) | All susceptible to amphotericin B and caspofungin. 98%–100% *C. albicans* and *parapsilosis* susceptible to fluconazole and voriconazole | ICU hospitalization, presence of central venous catheter, GI disorders, extremely low birth weight | | | Fluconazole (57%) amphotericin B (25%) |
| Pappas et al. [22] | USA | 1995–1997 | 144 children (<1 year, $n = 91$) | *C. albicans* (49), *C. parapsilosis* (34), *C. tropicalis* (8), *C. glabrata* (6) | | Intravascular catheter, antimicrobial therapy, TPN, endotracheal intubation, corticosteroid therapy, surgery | Neutropenia, tracheal intubation, no difference between *C. albicans* and *C. parapsilosis* | 23 | Amphotericin B (61%) fluconazole (15%) both (17%) |
| Pasqualoto et al. [33] | Brazil | 1995–2003 | 78 children (19 neonates) | *C. parapsilosis* (38.5), *C. albicans* (21.8), *C. tropicalis* (21.8) | | Broad-spectrum antibiotics, ICU, vasopressors, blood transfusions, arterial catheters, chest tube, cardiothoracic surgery, mechanical ventilation, parenteral nutrition (neonates: prematurity, birth weight) | | 24 | Amphotericin B |
| Pasqualotto et al. [34] | Brazil | 1995–2003 | 61 children plus catheter (14 neonates) | *C. parapsilosis* (32.8), *C. albicans* (20), *C. tropicalis* (24.6), *C. krusei* (3.3), *C. glabrata* (1.6) | | Underlying diseases (congenital malformations and malignancies, prematurity (neonates) | *Early death*: failure to remove CVC, severity of infection, lack of antifungal therapy. *late death*: hypotension, lung injury, azotemia, severity of infection | 47.5; CVC maintenance *vs* removal 90 *vs* 39.2% | |
| Avila-Aguero et al. [23] | Costa Rica | 1994–1998 | 110 neonates | *C. albicans* (90) *C. tropicalis* (10) | | Previous use of antibiotics, central catheters, parenteral nutrition, tracheal intubation, prematurity | No differences | 34 | Amphotericin B (100%) + fluconazole (14%) |

**Table 3** continued

| Reference | Country of origin | Study period | No of cases | *Candida* spp (%) | Susceptibility test (S %) | Risk factors for candidemia | Risk factor for mortality | Mortality (%) | Therapeutic choices |
|---|---|---|---|---|---|---|---|---|---|
| Blyth et al. [5] | Australia | 2001–2003 | 33 neonates | *C. parapsilosis* (42,4), *C. albicans* (39.4), *C. glabrata* (9.1) *C. tropicalis* (3) *C. dubliniensis* (3) | All susceptible to fluconazole | Prematurity (93.4) hyperalimentation (93.9) ICU admission (93.9) vascular access device in situ (88.9) previous antibacterial therapy (96.3) | Not found | 22 | Amphotericin B (86.4%) fluconazole (63.6%) |
| Badran et al. [24] | Jordan | 1995–2006 | 24 neonates | *C. albicans* (50), *C. krusei* (20), *C. glabrata* (10) *C. tropicalis* (10) | | GI pathology, antibiotic use, central line use of intralipids, previous bacterial sepsis | Duration of total hospitalization | 54.2 | Fluconazole (43%) amphotericin B (24%) both (24%) |
| Kuzucu et al. [25] | Turkey | 2003–2004 | 16 pediatric and 5 neonatal ICU | *C. albicans* (42) *C. parapsilosis* (30), *C. pelliculosa* (21), *C. famata* (10) | Amphotericin B (100), fluconazole (93), itraconazole (82) | Broad-spectrum antibiotics, mechanical ventilation, TPN, CVC, underlying conditions | | 76 | Amphotericin B (84%), fluconazole (16%) |
| Rodriguez et al. [34] | Spain | 2002–2003 | 24 neonates | *C. parapsilosis* (67), *C. albicans* (29), *C. glabrata* (4) | All susceptible to fluconazole, flucytosine, amphotericin B | Low birth weight, prematurity, CVC, previous antibiotic therapy, TPN, mechanical ventilation, antifungal treatment | | 21 | Amphotericin B (92%) |
| López Sastre et al. [26] | Spain | 1997–1998 | 79 neonates | *C. albicans* (45.6), *C. parapsilosis* (32.9), *C. tropicalis* (10.1) | | Very low birth weight | | 10.2 | Amphotericin B (liposomal) |
| Roilides et al. [27] | Greece | 1994–2000 | 58 neonates | *C. albicans* (65.5), *C. parapsilosis* (15.5), *C. tropicalis* (7) | Amphotericin B (100), azoles (97.5) | CVC, TPN, corticosteroid therapy, previous antimicrobial therapy, previous surgery. No significant differences between neonates infected with *C. albicans* and those infected with *C. parapsilosis* | *C. albicans* vs. *C. parapsilosis* infection | 29 | Amphotericin B |

*ICU* intensive care unit, *CVC* central venous catheters, *TPN* total parenteral nutrition, *GI* gastrointestinal, *DIC* disseminated intravascular coagulation

kidneys, liver, and spleen and demonstrates fungostatic activity against *Candida* spp [6]. Nevertheless, in the clinical setting, precaution should be taken to ensure adjusting dosing and prompt identification of adverse events, even rare, such as visual effects and liver toxicity [36]. Also, caspofungin demonstrates high in vitro antifungal activity, although in clinical use it has some disadvantages due to poor penetration through uninflamed meninges and ocular vitreous [6]. In our NICU, use of lipid formulations of amphotericin B is more favored for candidemia treatment, whereas, recently, caspofungin is used in selected cases. In a recent survey that took place in Greece, amphotericin B was the drug of choice for treating neonatal candidiasis [37]. As shown on Table 3, amphotericin B and to a lesser extent fluconazole are preferred for neonatal candidemia treatment [5, 19, 22, 23, 25–27, 34].

During the study period, thirteen persistent candidemia cases (32.5%) were identified, although the in vitro resistance to antifungal drugs was very low. Persistence of infection despite treatment with an appropriate dosage of an active agent is well recognized. It is attributed to neonate's immune status that is unable to eliminate the fungus [13]. In previous studies, persistent candidemia was observed in 10% of ELBW infants [12, 13], was associated with non-*albicans* infection [38] and exhibited a poor outcome [13]. In our setting, there is no difference in *Candida* spp isolates (54% due to *C. albicans* and 46% due to *C. parapsilosis*), whereas, the mortality rate is not higher that overall mortality (23 vs. 35.7%).

Risk factors associated with candidemia in NICU have been well characterized [6, 13, 39] and were common in the present study. Almost all patients had at least one identifiable risk factor, such as, low birth weight (85%), low gestational age (82.5%), previous use of antibiotics and steroids (90%), use of central indwelling catheters (75%), endotracheal intubation (80%), total parenteral nutrition (95%), previous bacteremia (100%), gastrointestinal pathology such as necrotizing enterocolitis (12.5%), respiratory disorders (47.5%), jaundice (25%), CNS disorders (10%), heart and vessels malformations (15%), malformations of alimentary tract (7.5%), as well as, liver and renal failure (7.5%). As shown on Table 3, most studies focus on birth weight, gestational age, use of antibiotics and steroids, parenteral nutrition, presence of central venous catheters, endotracheal intubation, abdominal surgery, gastrointestinal tract disorders or colonization and length of ICU stay. Vaginal delivery as a risk factor is controversial [18, 20].

*C. albicans* is isolated at a higher rate in ELWB ($P < 0.01$) in our NICU, whereas in a large scale study, neonates with *C. parapsilosis* bloodstream infection were older than neonates with *C. albicans* infection ($P < 0.001$), [17]. In accordance with other studies, no statistically significant differences were observed between *C. albicans* and *Candida* non-*albicans* candidemia regarding presence of other risk factors [27].

Although low number of patients may restrict parameters with statistically significant results, low birth weight and low gestational age constitute significant determinants of candidemia outcome. The Expert Panel recommends routine fluconazole prophylaxis for premature infants and infants with extremely low birth weights in nurseries that have a high incidence of invasive candidiasis [35]. No prophylaxis is given to premature infants and infants with ELBW by our NICU personnel. Recent studies suggest that fluconazole prophylaxis may exert a beneficial effect on extremely preterm neonates even in nurseries with low candidemia incidence rates [40]. Also, emergence of natively fluconazole-resistant *Candida* spp should be taken into account, although existing data do not justify this theory [41]. Our data show no significant association between outcome and presence of endotracheal intubation, central lines, parenteral alimentation or other risk factors ($P > 0.05$). In previous reports, duration of hospitalization [24], surgery [27], endotracheal intubation [22], failure [33] or delay [19] to remove a catheter and lack of antifungal therapy [33] were associated with higher mortality rates in pediatric patients with candidemia. Although failure to remove catheters was an independent risk factor for early death, it had no impact on late death group (8–30 days after candidemia was diagnosed) [33].

In our setting, overall mortality is 35.7%, whereas in other studies, it varies from 10.2 [26] to 54.2% [24]. In accordance with other studies [22], no statistically significant difference is observed regarding outcome of *C. albicans* versus outcome of *Candida* non-*albicans* candidemia. Nevertheless, *C. albicans* association with higher mortality rates in neonates has been described [14, 27]. Interestingly, in our setting, *C. albicans* is isolated at a higher rate, eleven among twelve candidemia cases involving ELWB ($P < 0.01$), exhibiting high mortality rate (73%). In the ELBW group, no case

is attributed to *C. parapsilosis* candidemia. In contrast, in the case of neonates more than 1,000 g, *C. parapsilosis* is associated with higher mortality rate (40%) than *C. albicans* (12.5%), ($P > 0.05$).

In conclusion, *C. albicans* represents the most common *Candida* (67.5%), isolated from candidemia cases in our NICU, followed by *C. parapsilosis* (25%). Resistance to antifungal agents is rare and involves mainly azoles. *C. albicans* is most often isolated from ELBW neonates as compared to non-*albicans Candida* ($P < 0.01$). ELBW and low gestational age are associated with poor outcome ($P < 0.01$). Taking into account the high mortality rates of neonatal candidemia and the high cost of hospital care [42], therapeutic approach should be multifaceted. It should include prevention by improving infection control practices and antimicrobial stewardship strategies [43], identification, and if possible, elimination of predisposing factors, as well as, early diagnosis and prompt appropriate treatment according to current guidelines and epidemiologic trends.

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