


# Epidemiology of Invasive Fungal Infections at Two Tertiary Care Neonatal Intensive Care Units Over a 12-Year Period (2000-2011)

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## Abstract

We conducted a retrospective review of 168 patients with invasive fungal infections from January 2000 to December 2011 in 2 neonatal intensive care units. Patients with *Candida* bloodstream infection (BSI, n = 152) were further analyzed. *C. albicans* was the most common species overall (47%); however, there was an increase in non-*albicans* sp from 2006 to 2011. *Candida* BSI clearance rates were lower in extremely low birth weight infants (77% vs 93%,  $P = .01$ ) and in patients with *C. albicans* infections (77% vs 91%,  $P = .01$ ). Clearance rates improved from 2000 to 2005 (70% - 90%) to 2006 to 2011 (86% - 100%). Combination antifungal use increased during the later years (73% vs 49%,  $P < .05$ ) and in patients with end-organ dissemination (83% vs 54%,  $P < .05$ ). We concluded that extremely low birth weight infants and *C. albicans* infection are factors associated with nonclearance of *Candida* BSI. Successful clearance of *Candida* BSI improved in 2006 to 2011, perhaps due to increase in non-*albicans* species and the use of combination antifungals.

## Keywords

*Candida*, NICU, invasive fungal infections, clearance, dissemination

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## Introduction

Invasive fungal infections (IFIs) are an important cause of nosocomial infection in the neonates, especially the extremely premature infants given the immaturity of the immune system.<sup>1</sup> Infection from various fungi including *Candida*, *Aspergillus*, *Malassezia*, and *Blastomyces* sp have been reported in these patients.<sup>2</sup> *Candida* bloodstream infections (BSIs) remain the most common infection among all IFIs and is associated with significant mortality and adverse neurodevelopmental outcome.<sup>2,3</sup> While *C. albicans* remains the most commonly isolated species in most studies, infection with non-*albicans* species, especially *C. parapsilosis*, is increasingly being reported.<sup>4,5</sup> *C. albicans* is thought to be more virulent and has been associated with higher rates of end-organ dissemination and mortality as compared with non-*C. albicans* species.<sup>1,3,6</sup>

Given the high rates of morbidity and mortality associated with IFIs, appropriate antifungal therapy remains vital in the management of these patients. Amphotericin

B and fluconazole are the 2 most widely used antifungals for treatment of IFIs in neonates.<sup>7</sup> Over the past decade, fluconazole has been increasingly used as a prophylactic agent to prevent IFI in high-risk premature infants.<sup>7,8</sup> However, the impact of antifungal prophylaxis on the epidemiology of IFI in neonates is not well understood. In addition, other clinical variables including gestational age, birth weight, prior surgery, antimicrobial use, and presence of central venous catheters (CVCs) that may also affect the outcome of IFIs have not been studied extensively.<sup>9</sup>

The objective of our research was to study the epidemiology of IFIs including trends, outcome, clinical and

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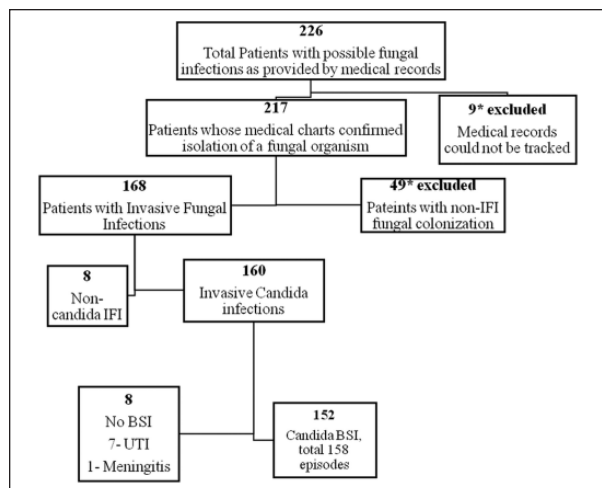
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**Figure 1.** Flowchart demonstrating selection of study patients and the types of invasive fungal infections (IFIs) seen. Non-Candida IFI: *Malassezia* sp (5), *Aspergillus* sp (2), and *Rhodotorula* sp (1). BSI, bloodstream infections.

laboratory characteristics, and antifungal utilization in our neonatal intensive care unit (NICU).

## Materials and Methods

We conducted a retrospective chart review of all patients diagnosed with IFI during their admission to the NICUs at the Detroit Medical Center. Our NICUs have a unique set-up, with a dual facility within the main hospital campus, one each at Hutzel Women's Hospital and at Children's Hospital of Michigan. The duration of study ranged from January 2000 until December 2011. Approval was obtained from the institutional review board at Wayne State University School of Medicine.

### Patient Selection

All patients with diagnoses of fungal infections including the terms such as invasive fungal infections, fungal infections, probable fungal infection, possible fungal infection, fungemia, candidiasis, candidemia, aspergillosis, fusarium, blastomycosis, and histomycosis were identified by the diagnoses list at discharge and the records of the hospital's microbiology laboratory that serves both the NICUs. Patients with *Candida* isolated from lung, stool, or skin were considered to be colonized and thus were excluded.

### Data Collection

**Demographic and Clinical Data.** Age, gender, race, underlying diagnosis, history of prematurity, predisposing

factors such as primary or acquired immunodeficiency, use of immunosuppressive agent, presence and type of CVC, prior surgical procedure, administration of total parenteral nutrition, and antibiotic usage prior to the onset of the fungal infection; type of fungal infection; degree of infection (dissemination); and use of prophylactic antifungal therapy. Results of cerebrospinal fluid analysis, echocardiography, abdominal ultrasound, and dilated eye exams were reviewed to assess for possible end-organ dissemination.

**Microbiological Data.** Culture results from blood, urine, and body fluids as appropriate were reviewed.

**Treatment Data.** Antifungal prophylaxis, empiric and definitive therapy with single or combination antifungal drugs were noted.

**Outcome Measures.** Primary outcome in the form of microbiologic clearance of infection or candidemia was recorded. Clearance was defined as sustained negative blood cultures for fungal species for 2 consecutive weeks with clinical improvement after therapy was initiated.

### Statistical Analysis

Descriptive statistics (mean, standard deviation, rate, ratio, and proportion) were used to characterize the study sample, including demographic factors (age, gender, race, age of diagnosis), types of infection, and utilization of antifungal medication. The incidence of IFIs before and after introduction of routine antifungal treatment were compared using  $\chi^2$  test with  $P < .05$  (2-sided). Time trend of IFIs was assessed by tabulating and plotting the total number of patients with IFIs per year over the study period from 2000 to 2011. Observed time trends were further assessed using Cochran-Armitage trend test.

## Results

A total of 226 patients were identified as having a possible fungal infection during the study period. Nine of these patients were excluded as their medical records were unavailable for further review. Of the remaining 217 patients, 49 patients were excluded after a detailed review of their medical records suggested fungal colonization rather than a true infection. One hundred and sixty-eight patients were eventually included in the study (Figure 1).

The overall incidence of IFIs in our NICUs was 9.8 per 1000 NICU admissions per year (range 2.7-20.2).

**Table 1.** Characteristics of IFIs (Non-*Candida* BSI) in the study populations.

| Variable                   | <i>Candida</i> UTI Without BSI (N = 7)              | <i>Candida</i> Meningitis (N = 1) | <i>Malassezia</i> (N = 5)              | <i>Aspergillus</i> (N = 2)          | <i>Rhodotorula</i> (N = 1) |
|----------------------------|---|-----------------------------------|--|-------------------------------------|----------------------------|
| Age (days), median (range) | 50 (27-150)   | 10                                | 90 (60-120)                            | 86 (22-150)                         | 50                         |
| Gender                     | Male: 7   | Female                            | Males: 3; females: 2                   | Male: 2                             | Female                     |
| Ethnicity                  | African American = 3<br>Caucasian = 2<br>Others = 2 | African American                  | African American: 4<br>Caucasian: 1    | African American: 1<br>Caucasian: 1 | African American           |
| Site of infection          | Urinary tract infection                             | CNS                               | Bloodstream infection                  | Pulmonary                           | Bloodstream infection      |
| Gestational age (weeks)    | <28 weeks: 5<br>28-32 weeks: 1<br>>32 weeks: 1      | 25 weeks                          | <28 weeks: 4<br>28-32 weeks: 1         | <28 weeks: 1<br>>32 weeks: 1        | 29 weeks                   |
| Birth weight (g)           | <1000: 4<br>1000-1500: 1<br>>1500: 2                | 730                               | <1000: 4<br>1000-1500: 1               | 1000-1500: 1<br>>1500: 1            | 1085                       |
| Risk factors               | Urinary catheter = 7                                | CVC, TPN, ABx                     | TPN: 5                                 | Immunodeficiency (I), ABx (I)       | TPN, ABx                   |
| Antifungals used           | C-AMB = 2<br>L-AMB = 3<br>Fluconazole = 2           | C-AMB                             | C-AMB: 2<br>L-AMB: 2<br>Fluconazole: 1 | L-AMB: 2                            | L-AMB                      |
| Cure                       | 5 (71%)   | 1 (100%)                          | 5 (100%)                               | 1 (50%)                             | 1 (100%)                   |

Abbreviations: IFI, invasive fungal infection; BSI, bloodstream infection; UTI, urinary tract infection; CVC, central venous catheter; TPN, total parenteral nutrition; C-AMB, conventional amphotericin B deoxycholate; L-AMB, liposomal amphotericin B.

The predominant IFI seen in our study cohort was invasive candidiasis present in 160 patients (95.2%) of which majority (152/160) had *Candida* bloodstream infection (BSI). Other pathogens isolated were *Malassezia* sp (5), *Aspergillus* sp (2), and *Rhodotorula* sp (1). The demographic characteristics and the predominant clinical manifestations seen with different types of IFIs (non-*Candida* BSI) are shown in Table 1.

### Patients With *Candida* Invasive Fungal Infections

Of 160 patients, 8 patients had *Candida* IFIs without evidence of a *Candida* BSI. Of these, 7 patients had urinary tract infection (UTI) and one had meningitis due to *C albicans* (Figure 1). Of the 152 patients with *Candida* BSI, recurrent BSIs were seen in 6 patients, leading to a total of 158 episodes during the study period. As majority of IFIs were due to *Candida* BSI in our study group, we further studied the characteristics of this group of patients (Table 2).

### Patients With *Candida* BSI

The median age at diagnosis was 26 days (range: 4-390 days). The majority of these patients (74%) were African

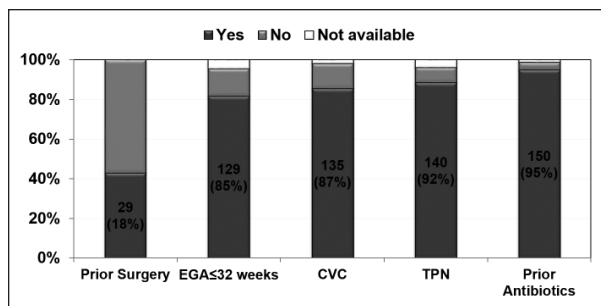
**Table 2.** Characteristics of Patients With *Candida* BSI (Candidemia) IFIs.

| Patient Characteristics (N = 152)              | Value          |
|--|----------------|
| Age (days), median (range)                     | 26 (4-390)     |
| Male gender (%)                                | 54             |
| Race   |                |
| African American (%)                           | 74             |
| Caucasian (%)                                  | 16             |
| Gestational age <sup>a</sup> , median (range)  | 28 (22-41)     |
| ≤28 weeks                                      | 70             |
| 29-32 weeks                                    | 18             |
| >32 weeks                                      | 12             |
| Birth weight (g) <sup>a</sup> , median (range) | 820 (400-5600) |
| <1000 g  | 61             |
| 1001-1500                                      | 20             |
| ≥1500 g  | 19             |

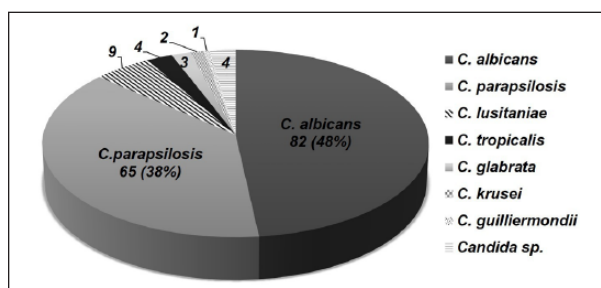
Abbreviations: BSI, bloodstream infection; IFI, invasive fungal infection.

<sup>a</sup>Data available for 151 episodes.

American, and the male-to-female ratio was 1.08:1. The median gestational age was 28 weeks (range: 22-41 weeks) with 70% of patients born at ≤28 weeks of gestation. The median birth weight of the study population was 820 g (range: 400-5600 g), with 61% patients categorized as extremely low birth weight (birth weight less



**Figure 2.** Associated risk factors for *Candida* BSI.



**Figure 3.** *Candida* species isolated during the study period.

than 1000 g). Most patients had one or more risk factors for IFI, with the most common factor being prior administration of antibiotics, which was seen in 95% patients (Figure 2). *C. albicans* accounted for 48% of the total isolates followed by *C. parapsilosis* (38%; Figure 3). Overall, non-*albicans* species accounted for 52% of *Candida* BSI.

Data on dissemination of candidemia to various organ systems was available in 126 patients. Of these, a third of patients (48/126) had one or more organ involvement as a result of *Candida* BSI. Kidney involvement based on sonographic demonstration of the presence of fungal balls was seen in 30 patients followed by meningitis in 12 patients, endocarditis in 8 patients, and various forms of eye involvement in 7 patients (endophthalmitis = 3, vitritis = 2, chorioretinitis = 2). Dissemination was significantly more common in patients with gestational age less ≤32 weeks ( $P = .04$ ; Table 3).

Median duration of antifungal treatment prior to documented clearance of candidemia was 5.5 days (range: 1–61 days). Table 4 presents the patient characteristics and factors associated with clearance and nonclearance of candidemia. Clearance of candidemia was documented in 132/158 episodes (84%). Significant risk factors associated with decreased clearance of candidemia were birth weight ≤1000 g ( $P = .01$ ) and infection with *C. albicans* species compared to non-*albicans* species ( $P = .004$ ). We also observed a trend toward increased rate

of clearance in patients with early removal of CVC within 3 days after diagnosis of candidemia, although this was not statistically significant ( $P = .07$ ). Of the 26 patients in whom nonclearance was documented, mortality was 100% within 5 days of the last positive culture for *Candida*.

The mean duration of antifungal treatment in patients with candida BSI was  $23 \pm 14$  days (range: 1 day to 92 days). Among 58 patients treated with various amphotericin B formulations, 25 patients received conventional amphotericin B (amphotericin B deoxycholate), 30 patients received amphotericin B lipid complex (lipid formulation in hospital drug formulary), and 3 patients received liposomal amphotericin B. Over half of the patients received a combination of 2 or more antifungal agents (90/158, 57%). Amphotericin B and fluconazole were the most common combination antifungal therapy used (45/158, 28%). The rates of combination therapy were higher in those patients with organ dissemination (83%) versus those without (54%;  $P = .004$ ).

### Time Trends of *Candida* Bloodstream Infection

There was a decreasing trend in the incidence of *Candida* BSI from 2003 to 2011 (Figure 4). Incidence data prior to 2003 were not available. A change in species distribution was also noted with decrease in *C. albicans* infection over the last 5 years of the study (except in 2010); however, this trend did not achieve statistical significance ( $P = >.05$ ; Figure 5). The clearance rates for *Candida* BSI improved from about 70% during the early part of the study to almost 100% over the last 5 years ( $P = <.01$ ; Figure 6). We also noted a trend toward increasing use of combination therapy from 38% in the first half of the study period to 70% or more in the latter part of the study ( $P = <.05$ ; Figure 7).

### Discussion

IFIs are important infections in our NICUs, with *Candida* BSI being the most common IFI. In our population, more than 80% of the *Candida* BSIs were seen in neonates with birth weight of <1500 g, which is consistent with published literature.<sup>3,10,11</sup> Apart from birth weight, there are several other risk factors associated with invasive IFI in neonates. The National Mycosis Survey study group enrolled 2847 infants from 6 Level 3 NICUs and highlighted various factors that independently predicted higher risk for invasive candidiasis after adjusting for birth weight.<sup>11</sup> Several of these risk factors were also noted in our study including prior antibiotic use, presence of CVC, parenteral nutrition,

**Table 3.** Factors Associated With Dissemination of *Candida* BSI (Dissemination Data Were Available in 126 Patients).

| Variable                                | Dissemination = 48,<br>n (%) | No Dissemination = 78,<br>n (%) | $\chi^2$       | P Value |
|---|------------------------------|---------------------------------|----------------|---------|
| Age $\leq$ 28 days                      | 31 (65)                      | 38 (49)                         | 3.019          | .08     |
| Male gender                             | 24 (50)                      | 42 (54)                         | 0.176          | .68     |
| EGA $\leq$ 32 weeks <sup>a</sup>        | 45 (96)                      | 59 (82)                         | — <sup>b</sup> | .04     |
| Birth weight $\leq$ 1000 g <sup>a</sup> | 28 (61)                      | 45 (62)                         | 0.005          | .92     |
| Early removal of CVC                    | 35 (72)                      | 57 (73)                         | 0.000          | .98     |
| <i>Candida albicans</i> species         | 25 (52)                      | 32 (41)                         | 1.467          | .22     |
| Clearance of infection                  | 41 (85)                      | 65 (83)                         | 0.097          | .75     |

**Table 4.** Patient Characteristics and Factors Associated With Clearance and Nonclearance of *Candida* BSI.

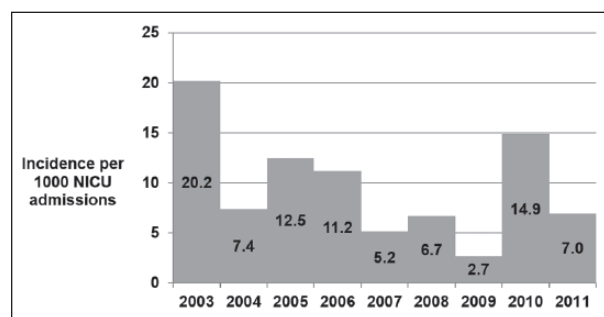
| Variable  | Clearance = 132,<br>n (%) | Nonclearance = 26,<br>n (%) | $\chi^2$       | P Value |
|---|---------------------------|-----------------------------|----------------|---------|
| Age $\leq$ 28 days                                | 70 (53)                   | 13 (50)                     | 0.080          | .77     |
| Male gender                                       | 72 (55)                   | 13 (26)                     | 0.181          | .67     |
| EGA $\leq$ 32 weeks <sup>c</sup>                  | 111 (87)                  | 22 (92)                     | — <sup>b</sup> | .55     |
| Birth weight $\leq$ 1000 <sup>c</sup>             | 72 (57)                   | 20 (83)                     | — <sup>b</sup> | .01     |
| Early removal (within 3 days of diagnosis) of CVC | 37 (41)                   | 2 (14)                      | — <sup>b</sup> | .07     |
| <i>Candida albicans</i> species                   | 56 (42)                   | 19 (73)                     | 8.185          | .004    |
| Age $\leq$ 28 days                                | 70 (53)                   | 13 (50)                     | 0.080          | .77     |

Abbreviations: BSI, bloodstream infection; EGA, estimated gestational age; CVC, central venous catheter.

<sup>a</sup>Data not available for 3 patients.

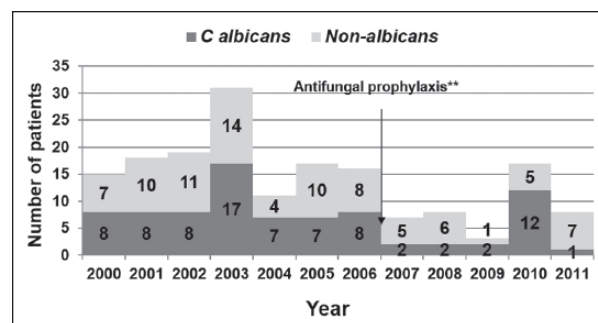
<sup>b</sup>Fisher exact test.

<sup>c</sup>Data not available for 7 episodes.



**Figure 4.** Incidence of *Candida* BSI from 2003 to 2011. A negative trend (0.9/1000 annual reduction),  $P = .218$ .

gestational age  $<$ 32 weeks, and prior abdominal surgery. The incidence of IFI, in general, as well as of *Candida* infections, varies across different NICUs. Incidence has been reported to be much higher in studies from outside the United States.<sup>12,13</sup> The higher incidence of IFIs in our study of 9.8 per 1000 NICU admissions per year is likely reflective of the tertiary care nature of our ICU, which often receives sick infants from other centers, and hence may have overestimated the total incidence of IFIs in our neonatal population.

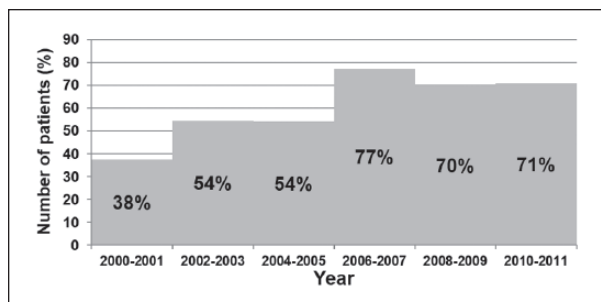


**Figure 5.** Trend of *Candida* species over study period. Cochran-Armitage trend test:  $Z = 0.34$ ,  $P > .05$ .

One patient had 3 episodes of *C. albicans* with prolonged NICU stay in 2010.

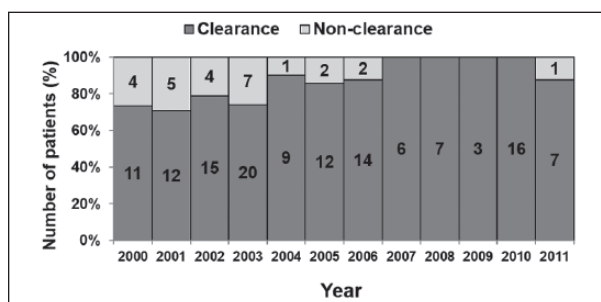
Antifungal prophylaxis started in 2007; fluconazole prophylaxis given in selected high-risk patients  $<$ 1500 g.

*Candida albicans* was the most common isolate in our NICUs followed closely by *C. parapsilosis*. Most studies conducted in the neonatal population have reported *C. albicans* to be the predominant species causing IFI.<sup>4,6,14</sup> Although *C. parapsilosis* was the second most common IFI in our patients, it has been reported to be the leading *Candida* species in other NICU settings.<sup>15</sup>



**Figure 6.** Trend of *Candida* BSI clearance over study period.

Cochran-Armitage trend test:  $Z = 3.017$ ,  $P < .01$ .



**Figure 7.** Combination antifungal use during the study period.

Cochran-Armitage trend test:  $Z = 2.92$ ,  $P < .05$ .

In our study, we observed that during the 12-year study period, the proportion of IFIs due to *C parapsilosis* increased compared to those with *C albicans*, a pattern also noted by other investigators.<sup>14,16</sup> This change in epidemiological trend has been associated with the use of fluconazole prophylaxis in the high-risk NICU babies. In our NICUs, routine fluconazole prophylaxis in high-risk premature infants was implemented in 2006, which likely contributed to the decreasing temporal trend of *Candida* IFI noted in our study, with a notable decline in *C albicans*.

Dissemination of *Candida* infection to end organs has been associated with poorer outcome.<sup>17</sup> Dissemination is more common among infants with birth weight <1500 g, a factor seen in almost 80% of our study population, leading to a relatively high dissemination rate of 38% in our study compared to other studies of up to 17%.<sup>1,17</sup> In our study, we also noted that infants with estimated gestational age  $\leq 32$  weeks were more likely to have end-organ dissemination than those born closer to term. The most common organs where dissemination occurred were the kidneys and central nervous system, as was also noted by other investigators.<sup>1,2,5,6,17</sup> The rate of clearance of *Candida* BSI in our study was comparable in patients

with and without dissemination to end organs, although combination antifungals were more likely to be used in patients with end-organ dissemination. This could be related to the perceived severity of infection in patients with end-organ dissemination leading to more aggressive use of antifungal agents and eventually achieving a similar rate of clearance as those without end-organ dissemination. The choice of antifungal treatment in our population was largely dependent on the clinician's discretion, with susceptibility testing done only in a minority of cases. Routine antifungal susceptibility testing may contribute to judicious use of antifungal agents and possibly achieve higher rates of clearance.

Given the lack of randomized controlled trials on antifungal use in neonates, treatment of fungal infections in this population is mostly extrapolated from studies done in adults. In a survey conducted among members of Pediatric Infectious Disease Society and neonatologists, amphotericin B formulations were used for treatment of neonatal candidemia by the majority (80%) of respondents.<sup>18</sup> It was also the most widely used agent in our study. With the availability of multiple antifungal agents with diverse mechanism of actions, there is potential for use of combination therapy that can broaden the overall antifungal coverage and potentially have synergistic effects. In our study, we noted a steady rise in the use of combination antifungals throughout the study period. It was interesting to note that this trend corresponded to the change in the epidemiological pattern of higher proportion of non-*C albicans* infection as well as with associated higher clearance. Given the retrospective nature of the study, it may be difficult to unravel the exact correlation between these observations.

The prognosis of infants with invasive *Candida* infections remains poor, with reported mortality rates of 40% to 50%.<sup>19-21</sup> In our study, the primary outcome was microbiologic clearance of infection or clearance of *Candida* BSI; however, we did not follow the course of the infants once clearance was achieved. Nevertheless, mortality within 5 day of the last positive blood culture for *Candida* was found in all 26 of 158 (16%) infants who did not have documented clearance of *Candida* infection in their bloodstream. This maybe an overestimate of *Candida*-related mortality since death may have been due to other causes and may have occurred before the actual documented clearance of *Candida* BSI. Nonetheless, clearance rates of *Candida* BSI improved significantly in the latter part of the study period, and corresponded to the use of combination antifungals as well as increased infection with non-*albicans* sp (*C parapsilosis*). Further work is necessary to establish if use of combination therapy is indeed associated with better outcome.

Strengths of our study include a large study population from a single medical center. The study also encompassed 12 years of data. However, our study has several limitations including its retrospective nature; results may not be representative of other NICUs across the country. Furthermore, treatment of IFIs is often individualized and can vary between treating neonatologists in consultation with infectious diseases experts. Treatment regimen may not always adhere to established protocols and treatment guidelines. Generalization of the treatment regimen is thus met with these limitations. Moreover, we did not study other factors such as the pharmacokinetics of the antifungal drugs and the associated comorbidities, which may have confounded the clearance of *Candida* infections.

In summary, *Candida* BSI was the most common form of fungal infection seen in our NICUs. End-organ dissemination was more common among infants born  $\leq 32$  weeks of gestation. Clearance of *Candida* BSI was lower in extremely low birth weight infants and among those with *C. albicans* infection. There is a trend toward an overall decline in the incidence of *Candida* infections in our NICU, with an increase in proportions of infection caused by non-*C. albicans* species. This, in addition to the increased use of combination antifungal therapies, may have contributed to an improvement in the clearance of *Candida* BSI in the recent years. Continued surveillance with multicenter studies and larger number of patients and long-term systematic follow-up is needed to better understand the optimal management of IFIs during the neonatal period.

### Author Contributions

RRA: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RLA: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

XC: Contributed to conception and design; contributed to analysis, or interpretation of data; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JLL: Contributed to conception and design; contributed to interpretation of data; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JYA: Contributed to conception and design; contributed to interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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