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Antifungal Susceptibility and Clinical Outcome in Neonatal Candidiasis

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Abstract

Background—Invasive candidiasis is an important cause of sepsis in extremely low birth weight infants (ELBW, <1000g), is often fatal, and frequently results in neurodevelopmental impairment (NDI) among survivors. We sought to assess the antifungal minimum inhibitory concentration (MIC) distribution for *Candida* in ELBW infants and evaluate the association between antifungal resistance and death or NDI.

Methods—This was a secondary analysis of the NICHD Neonatal Research Network study, "Early Diagnosis of Nosocomial Candidiasis". MIC values were determined for fluconazole, amphotericin B, and micafungin. NDI was assessed at 18–22 months adjusted age using the Bayley Scales of Infant Development (BSID). An infant was defined as having a resistant *Candida* isolate if ≥1 positive cultures from normally sterile sites (blood, cerebrospinal fluid or urine) were resistant to ≥1 antifungal agent. In addition to resistance status, we categorized fungal isolates according to MIC values (low and high). The association between death/NDI and MIC level was determined using logistic regression, controlling for gestational age (GA) and BSID (II or III).

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Results—Among 137 ELBW infants with IC, MICs were determined for 308 isolates from 110 (80%) infants. Three *Candida* isolates from 3 infants were resistant to fluconazole. None were resistant to amphotericin B or micafungin. No significant difference in death, NDI, or death/NDI between groups with low and high MICs was observed.

Conclusions—Antifungal resistance was rare among infecting *Candida* isolates, and MIC level was not associated with increased risk of death or NDI in this cohort of ELBW infants.

Keywords

Neonatal candidiasis; minimal inhibitory concentration; antifungal; mortality; neurodevelopmental impairment

Introduction

In premature infants, *Candida* is an important cause of late-onset sepsis.[1–3] Among extremely low birth weight (ELBW) infants (<1000 g birth weight), the incidence of invasive candidiasis (IC) varies across NICUs from 0.6% to 8%.[2,4–7] Consequences of IC in this population are severe with 14–40% mortality and 30–70% neurodevelopmental impairment (NDI) among survivors.[3,4,8,9] Amphotericin B deoxycholate or fluconazole are recommended as first line therapy; echinocandins, such as micafungin, are an alternate treatment option.[10]

The most common isolates among premature infants with IC are *C. albicans* and *C. parapsilosis,* organisms which are generally susceptible to first line antifungal therapy.[4,6,7] However, there has been increase of the proportion of non-*albicans Candida* which are associated with resistance to fluconazole.[6,11]

Candida resistance status is based on clinical breakpoints (CBPs), which are determined following consideration of drug pharmacokinetic (PK) and pharmacodynamic (PD) parameters, correlations between clinical outcomes and minimal inhibitory concentration (MIC), as well as MIC distributions of wild-type fungal isolates.[12] Clinical data supporting CBPs are usually derived from prospective antifungal trials primarily involving adults.[12,13] Antifungal PK are not the same between premature infants and adults.[14] Moreover, clinical course and outcome of IC differs in premature infants who are at higher risk of meningoencephalitis and NDI.[15–17] Therefore, correlation between antifungal MIC and clinical outcome may differ in premature infants compared to older children or adults. Studies assessing *Candida* susceptibility and clinical outcomes are limited by small sample size, or by combining infants and adults in the same cohort.[18–20] We therefore performed an analysis of data collected in the Neonatal Research Network *Candida* study to describe the antifungal MIC distribution for *Candida* in ELBW infants and to evaluate the association between antifungal resistance and death or NDI.

MATERIALS AND METHODS

Study population

This study included infants enrolled in the prospective NICHD-Neonatal Research Network (NRN) study, "*Neonatal Candidiasis: Epidemiology, Risk Factors, and Clinical Judgment*."[15] The objective of this former study was to identify risk factors for neonatal candidiasis. The study cohort included 1515 ELBW infants evaluated for possible sepsis between 3 and 120 days of life at 19 NRN sites from March 2004 through July 2007. In the current study, we included infants from this cohort diagnosed with IC. The Institutional Review Board at each center approved participation in the registry and the follow-up studies. Written informed consent for participation in the study was obtained from parents or legal guardians.

Definitions

We defined IC as having ≥1 positive cultures for *Candida* from blood, urine (obtained by catheterization or suprapubic aspiration), cerebrospinal fluid, or other sterile body source. Choice of antifungal therapy was at the discretion of the attending neonatologist and included amphotericin B deoxycholate, lipid complex amphotericin, micafungin, and fluconazole. Species were independently identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), and antifungal susceptibility testing was performed by broth microdilution according to the Clinical and Laboratory Standards Institute (CLSI) M27-A3 reference standard at the University of Texas Health Science Center at San Antonio Fungus Testing Laboratory.[21–23] An infant was categorized in the resistant group if he had ≥1 *Candida* isolate from a sterile body source that was resistant to ≥1 of the three antifungals tested. A *Candida* isolate was classified as resistant according to the clinical breakpoints in the CLSI M27-S4 document (Table 1).[24,25] Current MIC determination methods for amphotericin B generate a restricted range of MICs, precluding reliable discrimination between susceptible and resistant *Candida* isolates. We therefore considered an isolate likely resistant to amphotericin B if MIC was ≥2 mg/L as suggested by the CLSI.[23] There is no established fluconazole clinical breakpoint established for *C. guillermondii,* and no fluconazole and micafungin clinical breakpoints established for *C. lusitaniae.* The epidemiologic cut-off values were therefore used to identify strains with decreased susceptibility (Table 1).[25–27] In addition to resistance status based on clinical breakpoints, we categorized fungal isolates as having a low or a high MIC (Table 1). The high MIC cutoff value was defined as the MIC required to inhibit 90% of a given *Candida* species (MIC_{90}). For *Candida* species with ≤10 isolates, MIC_{90} could not be estimated, and the high MIC cutoff was defined as the epidemiologic cutoff value published in the literature. If an infant had multiple positive *Candida* cultures, the isolate with the highest MIC for a given antifungal, was used in the analysis.

The primary outcome of our analysis was the composite of death or NDI at 18–22 months of corrected age.[28,29] NDI evaluation included the Bayley Scales of Infant Development (BSID) II (for infants born before 2006) or III (Table 2). Secondary outcomes included length of hospital stay and therapy failure. Therapy failure was defined for infants treated with an antifungal drug within 3 days of first positive *Candida* culture, as any of: 1) death

within 14 days of therapy initiation, 2) end-organ involvement, and 3) persistent *Candida* infection defined by ≥1 positive blood or cerebral spinal fluid (CSF) cultures >14 days after therapy initiation. End-organ involvement was defined as the following: 1) at least 1 CSF positive culture for *Candida*, 2) ophthalmoscopy findings consistent with endophthalmitis, 3) echocardiography findings consistent with endocarditis or large sessile mass on the wall of the myocardium, and 4) echogenic findings consistent with abscesses in the liver, spleen or kidney.

Statistical Analysis

We described infants' baseline characteristics using median and range for continuous variables, and counts and proportions for categorical variables. The proportion of infants infected with ≥1 resistant *Candida* was also described at the infant level for each antifungal. *Candida* species, distribution of MIC and proportion of resistant isolates to each antifungal were described at the isolate level. MIC_{50} and MIC_{90}, defined as the MIC required to inhibit growth of 50 and 90% of the isolates for 1 given species, were described for each *Candida* species with >10 isolates available for analysis. We quantified variation in categorical outcomes (death or NDI, and therapy failure) related to *Candida* MIC (low and high; see table Supplemental Digital Content 1) and antifungal resistance, using logistic regression and adjusting for gestational age (GA) and being born before or after 2006 (cohort 1 or 2). In 2006, the Network Follow-Up study changed the psychometric instrument used to evaluate neurocognitive functioning from the BSID II to the BSID III. Among survivors, length of hospital stay was compared between infants with high MIC to any antifungal and those with only low MIC using the Wilcoxon rank-sum test. All statistical tests were 2-sided, with significance defined as $P<0.05$.

RESULTS

Among the 1515 infants enrolled, 137 (9%) developed IC, and 110/137 (80%) had MIC results (321 total *Candida* isolates from sterile sites) (Figure 1). Thirteen isolates were excluded from this analysis either because species identification was not successful (n=4), or *Candida* isolates could not be linked to a subject from the main analysis (n=9). Hence, the resulting number of *Candida* isolates used in this analysis was 308 from a total of 110 infants. Median (range) gestational age was 25 (23–29) weeks, and median postnatal age at first positive culture was 19 (4–84) days (see table Supplemental Digital Content 1). No difference in demographics were observed between infants with low and high MIC (see table Supplemental Digital Content 1).

Candida species and MIC distribution

Among 308 *Candida* isolates, the most frequent species were *C. albicans* (184 [60%]), *C. parapsilosis* (107 [35%]), and *C glabrata* (9 [3%]) (Table 3). Four infants had two different *Candida sp.*, leading to a total of 114 infant-*Candida sp.* Among those 114 infants-*Candida sp*, distribution of MIC suggested that fluconazole and amphotericin B MIC distributions were similar for *C. albicans* and *C. parapsilosis* (Figure 2). However, micafungin MIC values were higher for *C. parapsilosis* relative to *C. albicans* (Figure 2). Detailed MIC distributions for each antifungal are available in tables, Supplemental Digital Content 2–4.

All *Candida* isolates were susceptible to amphotericin B deoxycholate and micafungin (Table 3). Three *Candida* isolates (2 *C. albicans*, and 1 *C. glabrata*), each from a different infant, were resistant to fluconazole (MIC of 64 mg/L; Table 3). Those 3 infants were male, with gestational age ranging from 24 to 26 weeks, and were 5–81 days at first positive culture. None of them had received prior antifungal prophylaxis, and they were from 3 different sites.

Of the 110 infants, 46 (42%) infants had a high MIC to any antifungal. More specifically, 25 (23%), 0 (0), and 43 (39%) infants had a *Candida* isolate with a high MIC to fluconazole, amphotericin B deoxycholate, and micafungin, respectively. There was no significant difference in the number of infants with antifungal prophylaxis (nystatin or fluconazole), among infants with a high MIC to any antifungal (3 [7%]) versus those with only low MIC (6 [9%], p>0.73). Site proportions of *Candida* isolates with a high MIC to any antifungal were more variable for *C. parapsilosis* than for *C. albicans* (see figure, Supplemental Digital Content 5).

Outcomes

Nine infants (8%) were lost to follow-up by 18–22 months. Among the 101 infants with known status, 39 (39%) infants died by 18–22 months (Table 4A). Among 62 infants who survived, 20 (32%) had NDI; and two infants did not complete the evaluation. Among infants with complete data, 59 (60%) either died or had NDI by 18–22 months follow-up. Among infants with *C. albicans* and *parapsilosis* which are the most common species, 35 (59%) and 20 (61%) infants experienced death or NDI, respectively. All infants who had a *Candida* isolate with a fluconazole MIC ≥2 mg/L either died or had NDI (Figure 3). Among the 3 infants with a *Candida* isolate resistant to fluconazole, 2 died, while the third had NDI. Too few *Candida* isolates were resistant when using the clinical breakpoints (n=3) to allow the correlation between outcome and antifungal resistance. There was no significant difference in the rates of death, NDI, or death/NDI among infants with a high MIC to any antifungal, versus those with low MIC (Table 4A). This result still held after limiting the analysis to infants treated with fluconazole (Table 4B). We did not perform a subgroup analysis of clinical outcomes by micafungin MIC in the subgroup of infants who were actually treated with micafungin because of their limited number (n=8). Similarly, no subgroup analysis for amphotericin B was performed because no *Candida* isolates had a high MIC to that antifungal.

Among 60 infants who survived to follow-up at 18–22 months, median (range) length of hospital stay was 118 days (69–268), and median postmenstrual age at discharge was 41 weeks (37 – 65 weeks). There was no significant difference in length of stay between infants with high and low MIC, 114 days (76–268) versus 122 days (69–203), respectively, p=0.38, nor in postmenstrual age at discharge, 41 (37 – 65) weeks versus 42 (37 – 53) weeks, respectively, p=0.35. Nine (26%) out of 34 infants administered fluconazole experienced therapeutic failure. However, there was no significant difference in the rate of therapy failure between those with high versus low fluconazole MIC (Table 4B).

DISCUSSION

This study evaluated antifungal susceptibility to the three most common antifungals used in the NICU in a cohort of ELBW infants infected with *Candida*, and determined the correlation between MIC and clinical outcome. Antifungal resistance was uncommon in this large cohort of ELBW infants with invasive candidiasis, and higher MIC did not predict clinical outcome. *C. albicans* and *C. parapsilosis* were the two most frequent species causing invasive infection (>90%) in our cohort, consistent with previous reports.[2,4,6,7,18,30] Although *C. glabrata* was the third most frequent species, it represented only 3% of all species. This finding is consistent with previous publications in which it is significantly less frequent than in adults. [12,30]

MIC distribution for amphotericin B was clustered around 1 mg/L for all species. Our results are similar to amphotericin MIC results against *Candida* isolates previously described in 3 cohorts of neonates in which few (0 to 8%) *Candida* sp from normally sterile sites had an MIC ≥2 mg/L.[18,31,32] In a previous cohort of 322 premature infants (<1500g birth weight), all infecting and colonizing *Candida* isolates had an MIC <2 mg/L.[33] The amphotericin B MIC_{90} we observed for *C. albicans* and *C. parapsilosis* (1 mg/L for both species) was similar to that previously described in the cohort of 322 premature infants (0.125 and 1 mg/L for infecting and colonizing isolates, respectively).[34] Given that current methods for MIC determination do not reliably discriminate between *Candida* isolates susceptible and resistant to amphotericin B, the correlation between clinical outcome and amphotericin MIC cannot be detected.[23]

Fluconazole resistance was uncommon (3 [3%] infants) in this study. Previously described cohorts of premature infants have reported that no *Candida* isolates were resistant to fluconazole.[6,31,32,34–36] This difference may be explained by the change of clinical breakpoints in 2012 for *C. albicans, C. parapsilosis* and *C. tropicalis*. For these 3 species, the MIC cutoff for fluconazole resistance decreased from 64 to 8 mg/L.[37,38] Previous reports of fluconazole MIC against *Candida* species in premature infants were usually interpreted with previous CLSI breakpoints therefore possibly underestimating fluconazole resistance.

Micafungin susceptibility data against *Candida* isolates in premature infants are very limited. Reports of micafungin MIC values come from mixed populations, including neonates, children and adults. In a cohort of patients (infants and adults) with *C. parapsilosis* fungemia (330 isolates), 2.4% of isolates were resistant to micafungin with an MIC_{50} and MIC_{90} of 1 and 2 mg/L, respectively.[39] In a cohort of 200 children (0–15 years) with *Candida* fungemia, micafungin resistance occurred in 1% of both *C. albicans*, and *C. parapsilosis*. $MIC_{50/90}$ were 0.016/0.03 mg/L and 1/2 mg/L against *C. albicans*, and *C. parapsilosis*, respectively.[33] These results are similar to what we observed in our cohort of ELBW infants.

Infants with IC suffered high rates of mortality (39%) and NDI (33%). These findings were similar to previous studies of premature infants with invasive candidiasis where mortality of 22–41% and NDI incidence of 30% have been reported.[8,30] Invasive infection caused by *Candida* isolates with high MIC may reduce antifungal efficacy and increase time to clear the pathogen from the infected site. This is all the more significant in infants with

meningoencephalitis for whom antifungal penetration into the central nervous system may be insufficient against *Candida* species with decreased susceptibility. In the present study, the number of resistant *Candida* isolates was too small to detect a correlation between antifungal resistance and clinical outcome. We also analyzed outcomes by MIC, using high and low cutoff values to define susceptible ranges, but were unable to detect significant differences. Previous studies correlating *in vitro* susceptibility testing against *Candida* and clinical outcome have yielded conflicting results. In mixed cohorts including infants and adults (>90% adults) with *C. albicans* fungemia, all-cause 30-days mortality was increased when MIC was equal or superior to 4 mg/L.[40] In another cohort including infants and adults with *C. glabrata* fungemia, elevated MICs were associated with clinical failure.[41] Lastly, consistent with our results, data from a small, single-center study in 38 young infants failed to correlate antifungal MIC to clinical outcome in infants with candidemia.[18]

Our study is the first large cohort of infants <1000 g birth weight with data on resistant *Candida* isolates, using latest species-specific clinical breakpoints, and evaluating data on micafungin susceptibility. Limitations of this study include the lack of dosing information, and therefore we could not adjust our analysis for this important covariate. We speculate that fluconazole dosing was lower than doses currently recommended, based on PK studies published after the original NRN study.[42] Another limitation is that our primary analysis focused on the correlation of outcomes and MIC to any antifungal, regardless of the antifungal (single or combined therapy) that was used for definitive treatment. However, a subgroup analysis of those treated with fluconazole did not show a correlation of fluconazole MIC and outcomes. Because there was no infant who had high amphothericin B MIC, and because of the limited number of infants who were treated with micafungin, we could not perform this analysis for those 2 antifungals. Our ability to assess fluconazole therapy failure was limited by the small number of infants with high MIC who experienced this outcome and the lack of data on central line dwell time Of note, the Bayley score used to assess NDI changed over the study period, and some experts have expressed concern that the Bayley score III (cohort 2; 2006–07) underestimates disabilities.[43] However, all three infants with resistant isolates were in cohort 1, and were assessed with the Bayley score II. Finally, some infants were lost to follow-up. All these limitations may have impaired our ability to assess the effect of MIC on clinical outcome.

CONCLUSIONS

Antifungal resistance was rare among *Candida* isolates causing IC in ELBW infants. Infection with a *Candida* sp displaying high MIC was not associated with higher risk of death or NDI in this cohort of ELBW infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Participating NRN sites collected data and transmitted it to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis.

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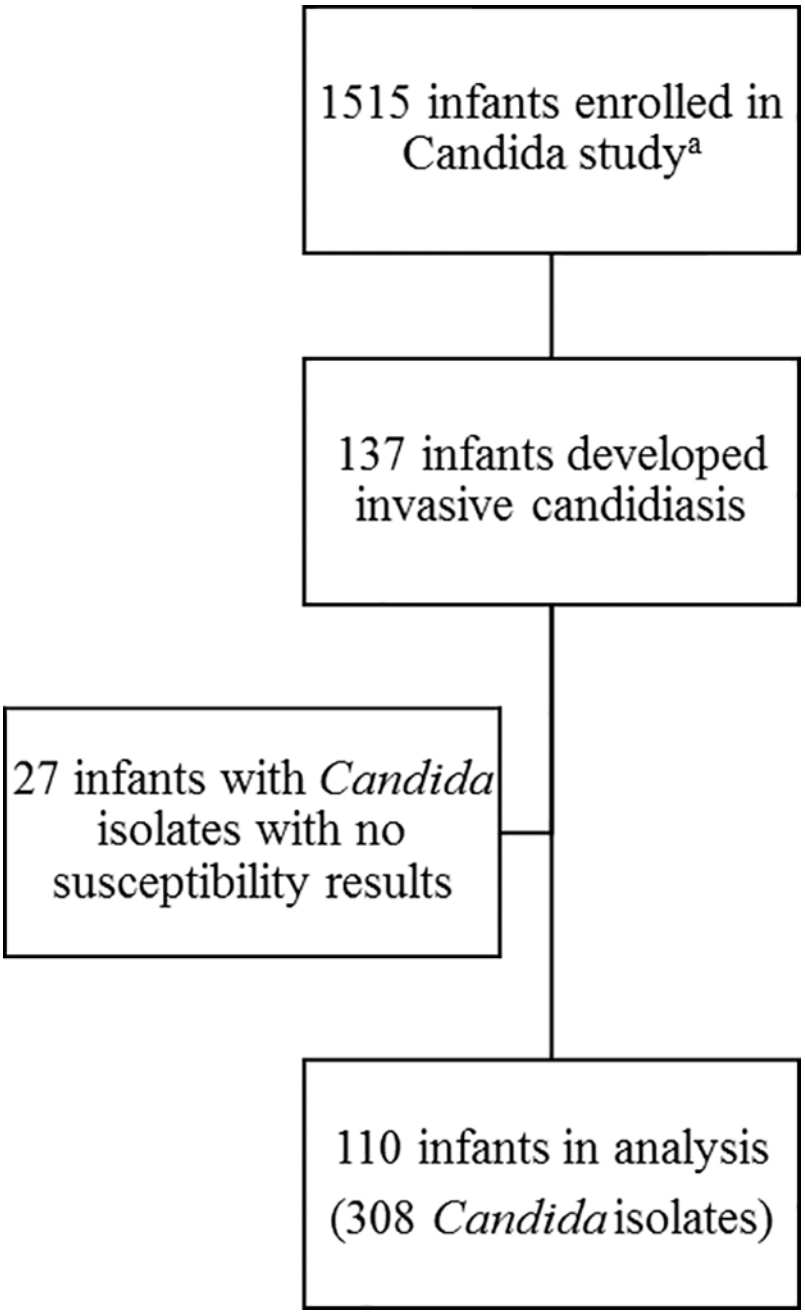


Figure 1.
Study enrollment flow chart
[a] In the original study[15]

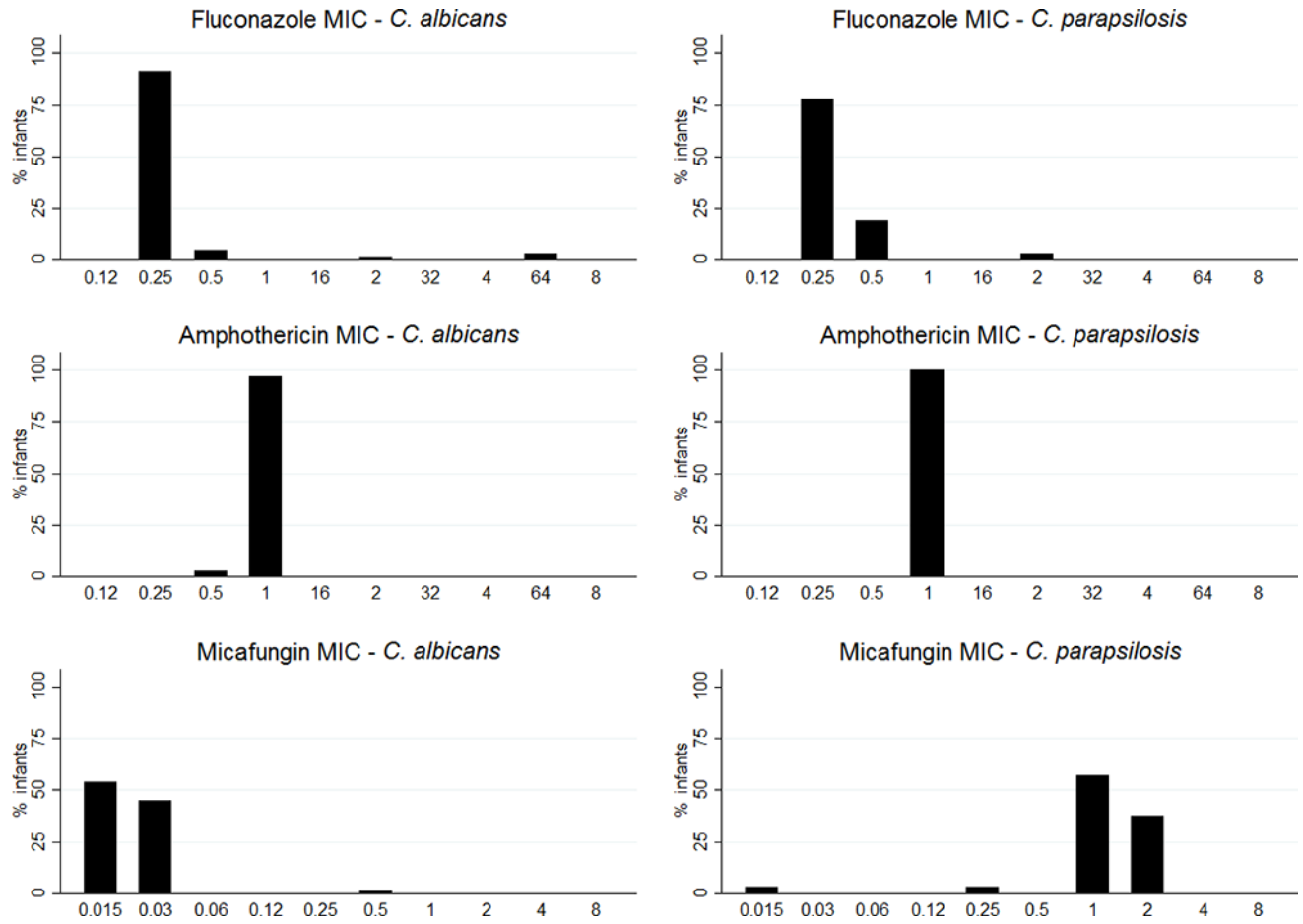
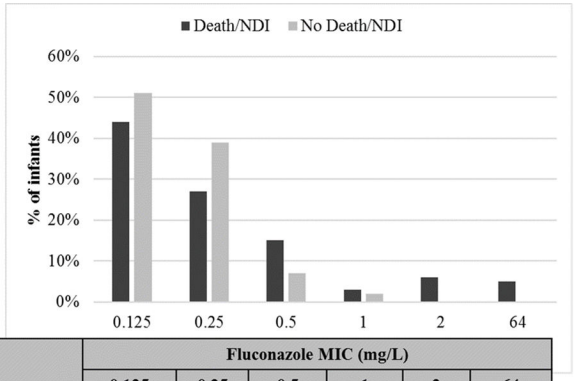


Figure 2.

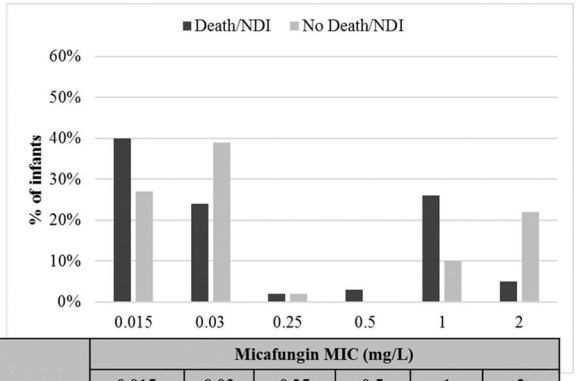
Distribution of infant Minimal inhibitory concentration (MIC) for *C. albicans* and *C. parapsilosis*[a]

[a]4 of 110 infants are counted twice in the subject breakdown as they each tested positive for two different Candida species

If an infant had multiple positive *Candida* cultures, the isolate with the highest MIC for a given antifungal, was used in the analysis.



	Fluconazole MIC (mg/L)					
	0.125	0.25	0.5	1	2	64
Death/NDI, n (N=62)	27	17	9	2	4	3
No death/NDI, n (N=41)	21	16	3	1	0	0



	Micafungin MIC (mg/L)					
	0.015	0.03	0.25	0.5	1	2
Death/NDI, n (N=62)	25	15	1	2	16	3
No death/NDI, n (N=41)	11	16	1	0	4	9

Figure 3.

Distribution of clinical outcomes by minimum inhibitory concentration (MIC) value[a, b]

NDI indicates neurodevelopment impairment; MIC: minimum inhibitory concentration

[a]4 of 110 infants are counted twice in the subject breakdown as they each tested positive for two different *Candida* species. If an infant had multiple positive *Candida* cultures, the isolate with the highest MIC for a given antifungal, was used in the analysis. Data on clinical outcomes missing for 11 infants.

[b]Figure for amphothericin B is not shown because all *Candida* isolates but 3 had an MIC of 1 mg/L

Table 1

Cut-off minimum inhibitory concentration values[13,23–27]

	Species	*Low MIC (mg/L)*	*High MIC*[a] *(mg/L)*	*Resistance breakpoint (mg/L)*
Fluconazole	*C.albicans*	≤0.125	≥0.25	≥8
	C. parapsilosis	≤0.25	≥0.5	≥8
	C. glabrata	≤16	≥32	≥64
	C. tropicalis	≤1	≥2	≥8
	C. guilliermondii	≤4	≥8	≥8[b]
	C. lusitaniae	≤1	≥2	≥2[b]
Amphotericin B	*All Candida species*	≤1	≥ 2	≥2[c]
Micafungin	*C. albicans*	≤0.015	≥0.03	≥1
	C. parapsilosis,	≤1	≥ 2	≥8
	C. glabrata	≤0.015	≥0.03	≥0.25
	C. tropicalis	≤0.06	≥0.12	≥1
	C. guilliermondii	≤1	≥ 2	≥8
	C. lusitaniae	≤0.25	≥ 0.5	≥ 0.5[b]

MIC indicates minimum inhibitory concentration

[a]Defined as the 90th percentile of MICs (MIC_{90}) for a given *Candida* specie with >10 isolates, or the epidemiological cutoff value from published literature if MIC_{90} could not be estimated in this study.

[b]There is no established fluconazole clinical breakpoint established for *C. guillermondii,* and no fluconazole and micafungin clinical breakpoints established for *C. lusitaniae*. The epidemiological cut-off values were therefore used to identify strains with decreased susceptibility

[c]There is no amphotericin B clinical breakpoint established for *Candida*. Isolates were considered likely resistant if MIC ≥2 mg/L

Table 2

Definition of Neurodevelopmental impairment (adapted from Wynn et al).[44]

	Cohort 1 (Infants born in 2004–05)	Cohort 2 (Infants born in 2006–07)
Neurologic impairment	Moderate to severe cerebral palsy	Moderate to severe cerebral palsy
Development	Bayley II MDI <70 or PDI <70	Bayley III cognitive <70 or GMFCS level ≥2
Vision	Bilateral blindness with no functional vision	<20–200 bilateral
Hearing	Bilateral amplification for permanent hearing loss	Permanent hearing loss that does not permit the child to understand directions of examiner and communicate despite amplification

Severe cerebral palsy defined as having a gross motor function classification system ≥2, MDI: mental development index, PDI: psychomotor development index.

Table 3

Isolate minimal inhibitory concentrations (MIC)

	Fluconazole			Amphotericin B			Micafungin		
Total number of isolates (number of infants)[a], N=308 (110)	**Range MIC (mg/L)**	**MIC 50/90 (mg/L)**	**N, Resistant**	**Range MIC (mg/L)**	**MIC 50/90 (mg/L)**	**N, Resistant**	**Range MIC (mg/L)**	**MIC 50/90 (mg/L)**	**N, Resistant**
***C. albicans*, n=184 (69)**	0.125 – 64	0.125/0.25	2	0.5 – 1	1/1	0	0.015 – 0.5	0.015/0.03	0
***C. parapsilosis*, n=107 (36)**	0.125 – 2	0.25/0.5	0	1	1/1	0	0.015 – 2	1/2	0
***C. glabrata*, n=9 (5)**	1 – 64	-	1	1	-	0	0.015 – 0.03	-	0
***C. guillermondii*, n=6 (2)**	0.5 – 2	-	0	1	-	0	0.5 – 1	-	0
***C. tropicalis*, n=1 (1)**	0.25	-	0	1	-	0	0.03	-	0
***C. lusitaniae*, n=1 (1)**	0.5	-	0	0.5	-	0	0.25	-	0

MIC indicates the minimal inhibitory concentration; MIC 50/90 the MIC values inhibiting 50% and 90% of all *Candida* isolates, respectively.

[a] 4 of 110 infants are counted twice in the subject breakdown as they each tested positive for two different *Candida* species.

Table 4

Outcomes by resistance status

A	**Invasive candidiasis (N=110) – All infants**		
	Infants with *Candida* isolate(s) having a low MIC[a] (n=46)	**Infants with *Candida* isolate(s) having a high MIC[a] (n=64)**	***P***
Death prior to discharge (%)[b]	15/46 (33)	21/64 (33)	0.88
Death at 18–22 months (%)[b]	17/44 (39)	22/57 (39)	0.93
NDI at 18-22 months(%)[c]	11/25 (44)	9/35 (26)	0.88
Death or NDI at 18–22 months (%)[c]	28/42 (67)	31/57 (54)	0.47
B	**Infants with invasive candidiasis and treated with fluconazole (N=34)**		
	Infants with *Candida* isolate(s) having a low fluconazole MIC[a] (n=26)	**Infants with *Candida* isolate(s) having a high fluconazole MIC[a]** (n=8)	*P*
Death prior to discharge (%)[b]	8/26 (31)	2/8 (38)	0.43
Death at 18-22 months (%)[b]	10/25 (40)	3/7 (43)	0.73
NDI at 18–22 months (%)[c]	3/14 (21)	1/4 (25)	0.57
Death or NDI at 18–22 months (%)[c]	13/24 (54)	4/7 (31)	0.27
Therapy Failure[b] (%)	5/25 (20)	4/8 (50)	0.19

[a] Low and high antifungal MIC defined in Table 1

[b] Adjusting for gestational age

[c] Adjusting for Bayley cohort and gestational age