Title: Neonatal invasive candidiasis in low-and-middle-income countries: data from the NeoOBS study

Short title: NIC in LMIC: the NeoOBS study

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Abstract

Neonatal invasive candidiasis (NIC) has significant morbidity and mortality. Reports have shown a different profile of those neonates affected with NIC and of fluconazole resistant *Candida* spp. isolates in low-and-middle-income -countries (LMICs) compared to high-income-countries (HIC). We describe the epidemiology, *Candida* spp. distribution, treatment and outcomes of neonates with NIC from LMICs enrolled in a global, prospective, longitudinal, observational cohort study (NeoOBS) of hospitalised infants <60 days postnatal age with sepsis (August 2018-February 2021).
127 neonates from 14 hospitals in 8 countries with *Candida* spp. isolated from blood culture were included. Median gestational age of affected neonates was 30 weeks (IQR: 28-34) and median birth weight was 1270g (IQR: 990 – 1692). Only a minority had high risk criteria, such as being born <28 weeks, 19% (24/127), or birth weight <1000g, 27% (34/127). The most common *Candida* species were *C. albicans* (n=45, 35%), *C. parapsilosis* (n=38, 30%) and *Candida auris* (n=18, 14%). The majority of *C. albicans* isolates were fluconazole susceptible, whereas 59% of *C. parapsilosis* isolates were fluconazole resistant. Amphotericin B was the most common antifungal used [74% (78/105)], followed by fluconazole [22% (23/105)]. Death by day 28 post-enrolment was 22% (28/127). To our knowledge, this is the largest multi-country cohort of NIC in LMICs. Most of the neonates would not have been considered at high risk for NIC in HICs. A substantial proportion of isolates was resistant to first choice fluconazole. Understanding the burden of NIC in LMIC is essential to guide future research and treatment guidelines.

Lay Summary

Our study describes neonates from LMIC with neonatal invasive candidiasis (NIC). Most of them were outside the groups considered at high risk for NIC described in HIC. *Candida s*pp. epidemiology was also different. The mortality was high (22%). Further research in these settings is required.

Introduction

The World Health Organisation (WHO) estimates that 2.4 million children died globally in the first month of life during 2019, with infection being the third commonest cause of death following prematurity and intrapartum-related complications[1]. The contribution of infection to deaths in the neonatal period is often underappreciated and varies according to geographic location, neonatal characteristics and whether or not neonates are born in a medical facility[2–4].

Neonatal invasive fungal infections are mostly caused by *Candida* spp. Reported rates of neonatal invasive candidiasis (NIC) vary significantly globally[5] and are associated with a high crude mortality rate, ranging from 12% to 37% in high-income countries (HICs) and from 8.9% to 75% in low- and middle-income countries (LMICs)[6]. In HICs, NIC is most commonly reported in neonates <1000 grams birth weight or <28 weeks gestational age, but recent reports from LMIC neonatal units show the occurrence of NIC outside these specific groups[3,7,8]. Although antifungal resistant *Candida* spp. infections remain uncommonn in HICs[9,10], LMICs are reporting an increasing proportion of fluconazole-resistant isolates, including *C. parapsilosis*[11,12], *C. krusei* and *C. auris*[13,14].

The aim of this NeoOBS invasive candidiasis sub-study was to describe the epidemiology, antifungal resistance patterns, antifungal treatment and clinical outcomes of neonates with *Candida* spp. bloodstream infections in LMICs. Data were collected as part of the larger NeoOBS study (https://clinicaltrials.gov/ct2/show/NCT03721302).

Materials and Methods

NeoOBS Study Population

NeoOBS, a global, prospective, longitudinal, observational cohort study of hospitalised infants <60 days postnatal age with sepsis, was conducted at 19 hospitals in 11 countries, between August 2018 and February 2020. Hospitals were a mix of tertiary and district hospitals, in Bangladesh (n=1), Brazil (n=2), China (n=3), Greece (n=1), India (n=3), Italy (n=1), Kenya (n=1), South Africa (n=3), Thailand (n=2), Uganda (n=1) and Vietnam (n=1) [15,16].

Infants could be enrolled into the study in two different ways (Figure 1). The primary cohort were infants enrolled with clinical sepsis meeting the diagnostic criteria of at least one clinical sign of sepsis plus one clinical or laboratory sign, with a blood culture taken prior to initiating new antimicrobial treatment (referred to as cohort 1). Up to 200 infants from each hospital were enrolled through this route. Infants were excluded if the clinical signs were subsequently deemed to be more likely related to a non-sepsis diagnosis, as determined by the treating clinician (supplemental table 1).

In addition, a secondary cohort of infants (referred to as cohort 2) were enrolled based on the isolation of a carbapenem-resistant organism (CRO) or *Candida* spp. from blood culture or with confirmed bacterial meningitis (supplemental table 1). Cohort 2 was designed to better understand specific infections and to capture infants with these infections who may not have been enrolled in or eligible for cohort 1. There was no minimum or maximum enrolment number for cohort 2 across hospitals. Infants already enrolled in cohort 1 were not eligible to be enrolled in cohort 2 as all microbiology findings were already captured as part of cohort 1 follow up.

Exclusion criteria for both cohorts were significant non-infectious related comorbidity expected to cause death within 72 hours, enrolled in an interventional study or previous enrolment in this study. Hospitals were given pragmatic flexibility for enrolment time frames given variability in case numbers and staffing capacity. Full inclusion and exclusion criteria for both cohorts is described in supplemental table 1.

Data collection

Infants meeting the eligibility criteria were enrolled from both cohorts. Infants in cohort 1 were followed prospectively daily for the duration of hospitalisation up to day 28 from the day of enrolment.
For infants in cohort 2, daily clinical and antimicrobial treatment data and any laboratory or microbiological investigations were retrospectively collected using medical notes and other available data from the day the culture was taken up to the day of enrolment, and then, prospectively collected from day of enrolment (supplemental figure 1) to 28 days from when the eligible blood culture was taken. For babies in both cohorts, clinical signs, supportive measures, and antimicrobial treatment were collected daily from the day of enrolment; blood culture, routine laboratory investigations and other microbiology results were collected as and when conducted. At enrolment, demographics, labour and delivery details and risk factors were collected.

All treatments and investigations were at the discretion of clinicians at the local hospital and were not determined by the study processes. At discharge or in-hospital death, information on mortality (if applicable), antimicrobial treatment, and both infection and non-infection related diagnoses were collected. Infants who were discharged prior to day 28 were telephoned on day 28, to assess vital status and any medical interventions since discharge. The primary outcome of the study was death by day 28, from the day the enrolment blood culture was taken. Primary and secondary causes (if applicable) of death were captured both for infants who died in hospital and those who died post-discharge before day 28.

Microbiological examinations were conducted as per local hospital procedures; however, babies must have had a blood culture taken prior to new antimicrobials being started to be eligible for enrolment in cohort 1. Blood culture results were collected as reported by local hospitals.

Study data were collected by paper case report form (CRF) and entered and managed using REDCap electronic data capture tools hosted at St. George's, University of London. REDCap is a secure, web-based software platform [17,18] used for the collection and management of research data.

Ethics approval from local and national bodies was received by each hospital prior to commencing recruitment. Informed consent was obtained for all patients prior to enrolment.

Candidemia study population

All infants enrolled in the NeoOBS study via either cohort 1 or cohort 2 who had a *Candida* spp. isolated from a blood culture at any point during their follow-up up to day 28 (regardless of enrolment diagnosis) were included in this analysis. Analyses were restricted to the first *Candida* spp. isolated from each patient. Regardless of when during follow up the *Candida* spp. was taken, all infants were censored at 28 days from when the enrolment blood culture for the overall NeoOBS study was taken (see supplemental figure 1) This means some infants may have contributed fewer than 28 days of follow up from when first *Candida* spp. culture was taken to this candidaemia sub-analysis.

Due to differing times in follow-up when *Candida* spp. cultures were taken for these patients, for this sub-analysis, all patients were aligned with day 0 defined as the day the positive *Candida* spp. blood culture was taken (Supplemental figure 1). All data collection tools were the same for infants in both cohorts. Analyses were restricted to infants from LMICs only, thus excluding infants from Greece (n=3) and Italy (n=0).

Statistical analysis

Categorical variables were described as relative frequency and continuous variables were described as median and interquartile range (IQR). Demographic and clinical characteristics between enrolment cohorts were compared using Chi-square test. Kaplan-Meier curves and Cox proportional hazards models were used to investigate mortality. All data management and analyses were conducted in RStudio v1.4.1717 (R version 4.0.3).

Results

Study population and baseline characteristics

After excluding infants from Greece and Italy, 3083 neonates were enrolled from 17 hospitals in cohort 1 and 166 neonates were enrolled from 14 hospitals in cohort 2. Results from the overall NeoOBS study are described elsewhere[19]. Overall, 127/3249 (4%) infants met the inclusion criteria for the candidemia sub-analysis (67 were from cohort 1 and 60 from cohort 2) (Figure 1). Infants with candidemia were from 14 hospitals in 8 LMICs; however, 85% (108/127) of the infants with candidemia were reported from 7 hospitals in three countries (South Africa, India and Vietnam). Forty six percent (58/127) of infants had *Candida* spp. isolated during follow up after enrolment into the overall NeoOBS study, while the remaining 54% (69/127) had *Candida* spp. isolated from their baseline enrolment blood culture.

At the time when the blood culture that grew *Candida* spp. was taken, the median postnatal age was 16 days (IQR: 10.5-21), the median gestational at birth age was 30 weeks (IQR: 28-34) and the median birth weight was 1270g (IQR: 990 – 1692). Fifty four percent (68/127) of the infants were male. Only 19% (24/127) of the infants were born before 28 weeks of gestation and 27% (34/127) had birth weights <1000g. Infants with candidemia were hospitalised for a median of 14 days (IQR: 6.5-20) prior to when the *Candida* spp. blood culture was taken. Eighty percent (102/127) of infants received at least one broad spectrum antibiotic in the week prior to that blood culture. The majority of cases, 90% (114/127), were born either at the enrolling hospital or in a referral hospital and remained hospitalised from birth. Baseline characteristics of both enrolment cohorts were similar (supplemental table 2). Epidemiological characteristics by survival are summarized in table 1.

Microbiology findings

The most common *Candida* species in this study were *Candida albicans* (n=45, 35%), *Candida parapsilosis* (n=38, 30%) and *Candida auris* (n=18, 14%). Other species isolated were *Candida glabrata* (n=6), *Candida pelliculosa* (n=4), *Candida tropicalis* (n=4), *Candida famata* (n=1), *Candida metapsilosis* (n=1), and *Candida rugosa* (n=1). There were 10 (8%) unspecified *Candida* spp. (Table 1). Species distribution varied by hospital (p<0.0001) and country (p<0.0001) (supplemental table 3). One patient had two *Candida* spp. isolates (*C. parapsilosis* and *C. glabrata*) from the same blood culture (total of 128 *Candida* spp. isolates). Sixty one percent (11/18) of *C. auris* isolates were found in India and the remaining 39% (7/18) were from South Africa.

Susceptibility testing was not reported for 13% (16/128) of isolates, and for 17 isolates (13%) only fluconazole susceptibility was reported. Susceptibility results for fluconazole, amphotericin B and an echinocandin [micafungin] were reported in 80% (103/128), 78% (87/128), and 36% (46/128) of all *Candida* spp. isolates, respectively (Figure 2). Of these, overall, 41/103 (40%) were fluconazole resistant, 16/87 (18%) were amphotericin B resistant and 0/46 (0%) were micafungin resistant.

Of the *C. albicans* isolates with susceptibility results reported, 91% (38/42) were susceptible to fluconazole, and 100% (30/30) were susceptible to amphotericin B; however, 15/45 (33%) did not have amphotericin B susceptibility reported.

Reported resistance to fluconazole in *C. parapsilosis* was high (19/32 resistant, 59%); however, the majority were susceptible to amphotericin B (27/29 susceptible, 93%). Almost all the fluconazole resistant *C. parapsilosis* isolates (17/19, 90%) were reported from South Africa.

There was an expected high reported resistance to fluconazole (15/17, 88%) and to amphotericin B (11/13, 85%) in *C. auris* isolates. Most *C. auris* isolates did not have micafungin susceptibility testing done (16/18, 89%). Resistance of *C. auris* isolates to voriconazole was reported in 31% (5/16). Figure 2 illustrates the susceptibility profiles of *Candida* spp. isolates to the three commonly used antifungal agents.

Antifungal drug use

Overall, 14% (18/127) of infants received antifungals for either prophylaxis (n=8) or empirical treatment (n=11) in the week preceding the positive blood culture with *Candida* spp. being taken. Of those, all the infants who received prophylaxis, received fluconazole. Of those receiving empirical treatment prior to the blood culture, Amphotericin B was received by 73% (8/11) of infants.

Overall, neonatal antifungal prophylaxis was uncommon in the infants that developed candidemia (8/127, 6%). None (0/27) of those born before 28 weeks of gestation, and only 3/34 (9%) of neonates with a birth weight less than 1000g received prophylaxis.

Ninety percent of infants (114/127) received antifungal treatment after taking the blood culture which grew *Candida* spp. including 8 infants who continued antifungal treatment that had been started before the culture (fluconazole: n=3, amphotericin B: n=5). Of the 106 who started any new antifungals after the blood culture was taken, only 1 had received fluconazole prophylaxis. After taking the blood culture, the median time to starting a new antifungal treatment in these 105 infants was 3 days (IQR: 2-4). The first antifungal treatment of choice was amphotericin B in 74% (78/105) and fluconazole in 22% (23/105) of the cases.

85/88 (97%) infants received appropriate antifungal treatment based on the reported *in vitro* susceptibility profile of the *Candida* species with available susceptibility testing results. In these infants, amphotericin B (n=45) was the most commonly prescribed antifungal, followed by fluconazole (n=27), voriconazole (n=10) and micafungin (n=3). In infants with known susceptibility profile of the *Candida* species, the median time to appropriate antifungal treatment was 3 days from when the blood culture was taken (IQR: 2-5 days, range: 8 days prior to blood culture to 12 days after blood culture).

Antifungal treatment varied by country (Figure 3) and causative *Candida* species (Figure 4). Amphotericin B was used in all countries. In infants who received antifungal treatment after blood culture, a higher proportion of infants received amphotericin B in South Africa (48/53, 91%) and

India (28/31, 90%) compared to Vietnam (5/13, 38%) (Figure 3). Fluconazole was less commonly prescribed in India (4/31, 13%) and South Africa (23/53, 43%) compared to Vietnam (9/13, 69%). Voriconazole was used only in India (n=10), micafungin was used predominantly in South Africa (n=10) and caspofungin was used only in Vietnam (n=1). Infants may have received more than one antifungal during their treatment.

Clinical outcome

Death by day 28 post-enrolment was 22% (28/127). Sixty four percent (81/127) of infants were still in hospital on day 28 post-enrolment. The median length of follow up from the day the *Candida* spp. culture was taken was 21 days (IQR: 11.5-27). Among infants who died, the median length of follow up was 7 days (IQR: 4-12.25). Unadjusted mortality by species is illustrated in Figure 5. In an univariable Cox proportional hazards analysis, mortality was strongly associated with birthweight <1000g (HR: 3.83; 95%CI: 1.84-7.97) and gestational age <28 weeks (HR: 2.32; 95% CI: 1.08-4.99). There was no significant difference in mortality by species, by hospital, by country or by study cohort (Table 2).

Discussion

To our knowledge, this is the largest multi-country cohort of neonates with *Candida* spp. bloodstream infections in the LMIC setting. Most of the neonates included in the NeoOBS invasive candidiasis sub-study, were outside the high-risk groups for NIC as described in HIC, with 81% born after 28 weeks' gestation and 73% with a birth weight >1000g. Although *C. albicans* was the most frequent species isolated, the species distribution varied significantly between hospitals and countries. Across the *Candida* spp. with known *in vitro* susceptibility profile, 40% were fluconazole resistant, 18% were amphotericin B resistant, while no resistance was reported for micafungin (albeit many isolates were not tested). *C. albicans* was reported to be highly susceptible to fluconazole and amphotericin B. In contrast, a significant proportion of *C. parapsilosis* was reported to be fluconazole resistant, driven by high resistance rates observed in South Africa[12]. *C. auris* was the third most common species overall but its presence varied greatly between countries. Amphotericin B was the most common empiric antifungal used (74%), followed by fluconazole (22%) with echinocandins rarely used. Antifungal prophylaxis was infrequently used in infants who developed candidemia, even for those neonates considered at high-risk. Overall, the mortality was high (22%), and was significantly associated with low birth weight (<1000g) and extreme prematurity (<28 weeks).

In the cohort of neonates with NIC described here, 37% weighed >1500g and 38% were ≥32 weeks of gestational age. These results are similar to other studies in LMIC [11,20], and contrast dramatically with the data from HICs, where extreme prematurity and ELBW neonates are the main high risk groups for NIC[21]. In 2018, for example, the DeNIS study reported unusually high rates of NIC in a cohort of neonates in India born outside the hospital; more than a quarter of neonates with a positive blood culture (90/339, 26.5%) had *Candida* spp. isolated. Remarkably, 61.5% of those neonates weighed more than 1500 g and 73.3% were born at or after 32 weeks' gestation[3].

C. albicans has been reported as the most common causative species in NIC[10,22]. Increasingly, a shift in epidemiology of NIC globally has been described, with a higher rate of non-*albicans Candida* isolates in LMICs compared to HICs[6]. The rise in non-*albicans Candida* spp. in NIC is associated with reduced susceptibility to fluconazole. This has been described in India, where MDR strains of *C. krusei* and *C. auris* have been reported[13]; and in South Africa[23], where surveillance has shown an increase in the number of fluconazole-resistant *C. parapsilosis*[12]. For example, Govender *et al*.

reported a significant shift towards *C. parapsilosis* in neonates, with 53% of all *C. parapsilosis* isolates being fluconazole-resistant and 44% and 70% cross-resistant to voriconazole and posaconazole respectively[12]. Other South African series report similar results[7,24,25] . In the cohort presented here, *C. albicans* and *C. parapsilosis* accounted for 35% and 30% of the isolates respectively. Whereas *C. albicans* remained mostly susceptible to fluconazole (91% cases), 59% of the *C. parapsilosis* isolates were fluconazole resistant, mostly from South Africa.

C. auris was the third most commonly reported pathogen (14% of all the cases) in this cohort, with significant variability between countries (0-27.5%). *C. auris* is a rapidly emerging, multi-drug resistant, nosocomial pathogen, with high reported resistance to fluconazole and amphotericin B [25–27]. There have been scant reports focused on invasive *C. auris* infections in neonates[28–30]; most of them are from India[28]. Chakabrati *et al*. published a multicentre prospective study from 2011-2012; where amongst 273 neonates from three hospitals with NIC, the proportion of *C. auris* isolates was 2.2% [13]. More recent data[11,14,28], together with our observations, show that *C. auris* has quickly become one of the most commonly encountered species causing NIC in LMICs.

Reported neonatal mortality attributable to NIC in LMICs varies from 20%[13] to as high as 50%[7,31]. In the cohort described here, mortality was strongly associated with low birth weight (<1000g) and gestational age (<28 weeks); however, we did not find a clear association with causative species or susceptibility profile.

Antifungal prophylaxis with fluconazole, targeted to neonates <1000g birth weight and/or <28 weeks gestation, as well as those infants with birth weight of 1000–1500g with additional risk factors, is a recommended strategy in neonatal units in HICs to prevent NIC[32–36]. Based on our data, NIC in LMICs affects mostly neonates with a birth weight >1500 grams, putting in doubt the relevance of HIC neonatal fungal prophylaxis guidelines for LMICs. In addition, a high prevalence of fluconazole resistance poses an important barrier to the use of fluconazole prophylaxis in these countries. Future studies determining the clinical and health economic benefit of neonatal antifungal prophylaxis in LMIC settings are needed. Fluconazole is not the only available drug to be considered; prophylaxis with nystatin, a low cost oral antifungal, which has also been proven to have an impact on neonatal mortality and is included in the Essential Medicines List (EML)[37–39] can also be considered.

Compared with the burden of bacterial sepsis, where *Klebsiella pneumoniae*, *Acinetobacter* spp. and *Escherichia coli* are the most commonly reported pathogens in LMICs[40,41], the burden of fungal sepsis, particularly caused by *Candida* spp. has been poorly described. For this reason, it is not possible to provide an accurate estimated burden of NIC in LMICs [6,11]. Reported incidence of invasive candidiasis in paediatric intensive care units is significantly higher in LMICs (42.7 cases per 1000 admissions) compared to HICs (0.043–0.47 cases per 1000 admissions)[6]. In general, *Candida* spp. are likely to be an underreported pathogen and mostly linked to healthcare-associated infections.

This study has some key limitations. First, not all neonates with *Candida* spp. bloodstream infections presenting at these hospitals were enrolled in the study, introducing risk of selection bias. The aims of the NeoOBS study were to describe presentation, management and outcomes of infants with sepsis not describe incidence of these infections thus we were unable to quantify incidence of NIC in this cohort due to this enrolment bias. It is also possible that the 7 hospitals contributing majority of the infants to this candidaemia cohort had higher repeat blood culture rates than other hospitals in the NeoOBS study. Cohort 2 enrolment may have missed some infants who died prior to a positive culture result and who were unable to be consented, potentially contributing survivor bias and lower mortality for certain *Candida* species. Differences in baseline characteristics and mortality between the two enrolment cohorts were explored (supplemental table 1) and no significant

differences were found in key risk factors, *Candida* species, or mortality, which supported combining patients from these two cohorts into one analysis. Additionally, we used hospital-reported identification and phenotypic susceptibility testing results for this analysis, which may be less accurate than MIC values and/or molecular identification techniques; moreover, the use of interpretation guidelines of antimicrobial resistance (e.g. CLSI, EUCAST, BSAC) may vary by hospital. Finally, there were a number of isolates that did not have any susceptibility testing done or were only tested for fluconazole. Therefore, we are unable to fully evaluate resistance and appropriateness of choice of the antifungal treatment.

In conclusion, this study demonstrates that NIC is associated with significant mortality in the LMIC setting. The optimal method of prevention and treatment of this life-threatening infection requires further targeted studies. These studies should consider the epidemiological differences of NIC in LMICs compared to HICs; with an increased incidence of NIC in neonates outside the "high-risk" group (<28 weeks and/or <1000 g) and, although with significant variability between settings, higher rates of fluconazole resistances in non-*albicans Candida* species. Insights into the fungal epidemiology and susceptibility profiles is of utmost relevance in order to develop management guidelines for NIC in LMICs. Diagnostics for *Candida* species, including susceptibility testing need to be made available and improved. Although no micafungin resistance was observed (within the few isolates tested), the role of empiric therapy with micafungin in LMICs for NIC needs to be a research priority. Micafungin has been included in the WHO Essential Medicine List for children in 2021[37], but there are still limitations for its use in neonates, such as the lack of defined optimal dose for those cases with meningoencephalitis[42,43]. Finally, studies in LMICs are required to define which neonates might benefit from antifungal prophylaxis. As our study shows, the current recommendations used in HIC targeting "high-risk" neonates do not entirely apply to neonates in LMICs.

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Disclosure of Conflict of Interest
There are no conflicts of interest to declare

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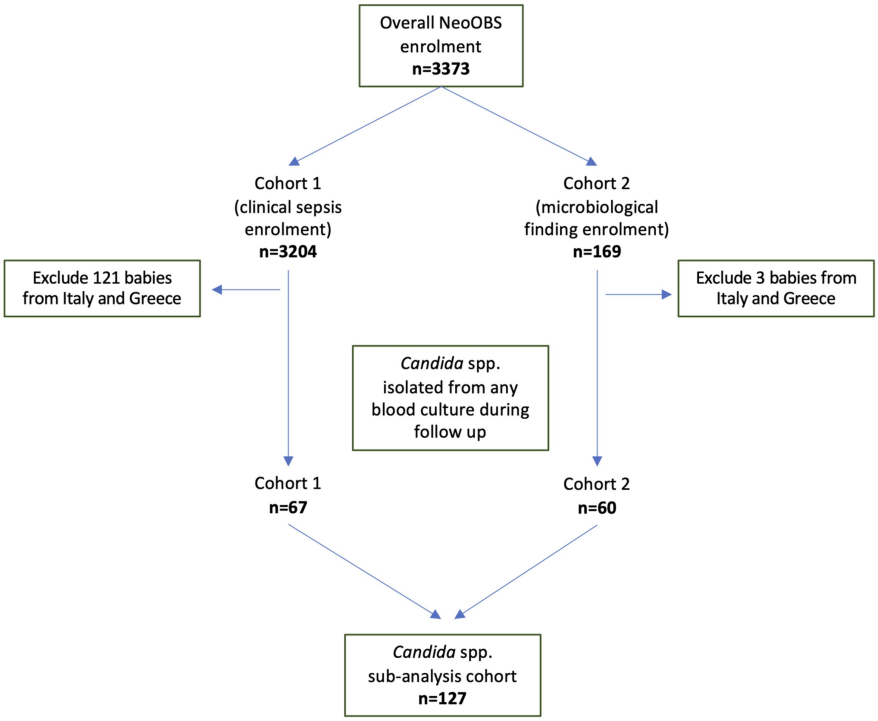

Figure 1. Candida spp. sub-study population derived from the overall NeoOBS study. See supplemental figure 1 for detailed schematic of the study population indicating the two enrolment cohorts.

Note: Overall NeoOBS enrolment: cohort 1 was 3204 babies from 19 hospitals in 11 countries; cohort 2 was 169 babies from 14 hospitals in 10 countries.

Candida sub-analysis cohort: cohort 1 includes 67 babies from 12 hospitals in 7 countries; cohort 2 was 60 babies from 12 hospitals in 7 countries.

Figure 2. Reported susceptibility profiles to amphotericin B, fluconazole and micafungin for the most common *Candida* species.

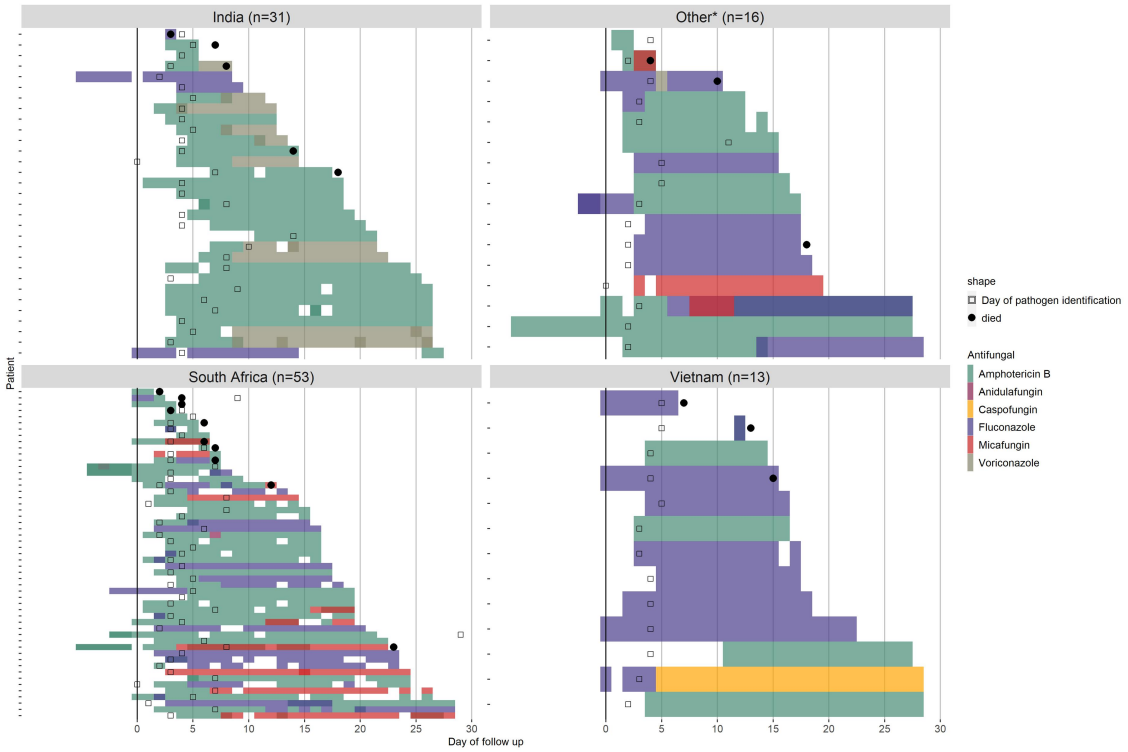

Figure 3. Patient-based antifungal treatment choice by country indicating the day the blood culture was taken (day 0), the day the fungal organism was identified (open squares) and mortality (solid dots). White space indicates calendar days that antifungal treatment was not given.

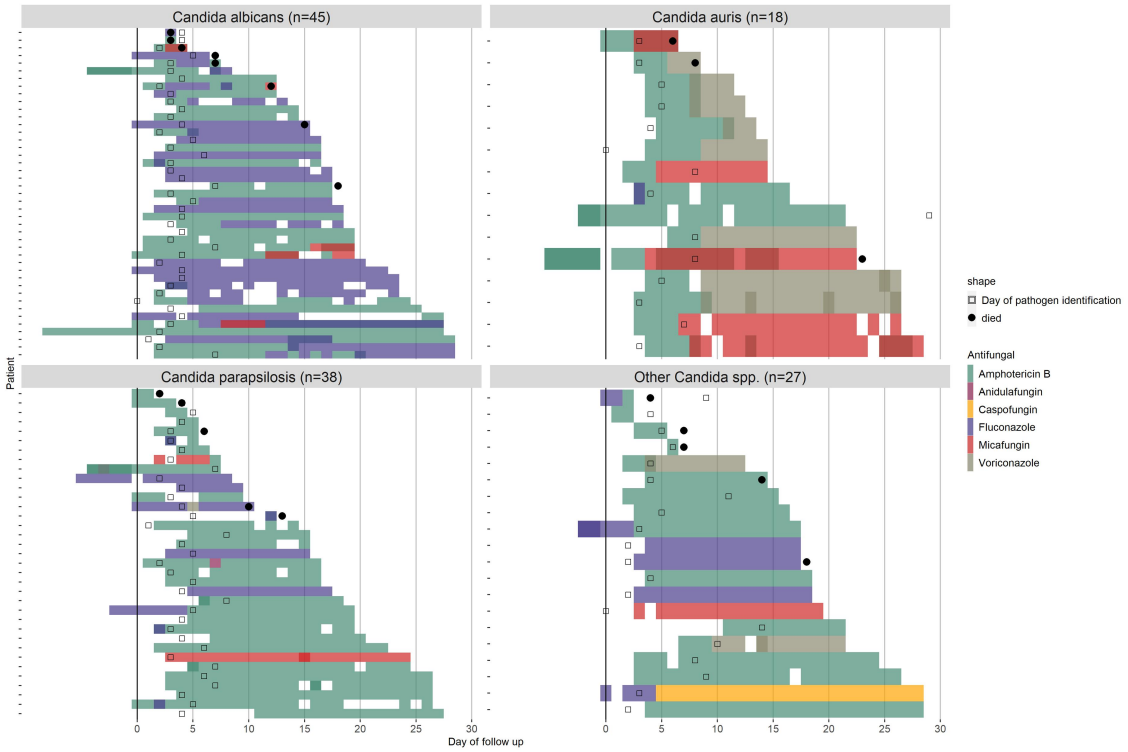

Figure 4. Patient-based antifungal treatment choice by causative Candida spp. Day 0 is the day the blood culture was taken which grew Candida spp. Day that the Candida spp. was identified is indicated with open squares, and mortality with solid dots.

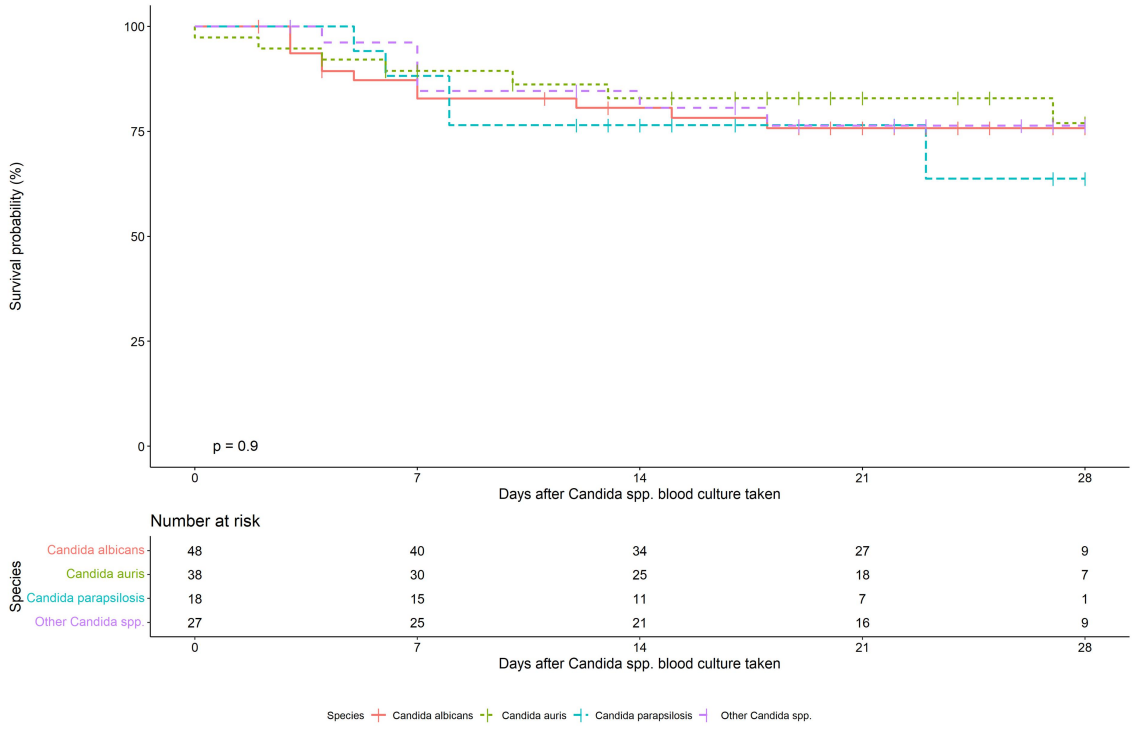

Figure 5. Kaplan-Meier curve for mortality from day of culture for each Candida species.

Table 1. Comparison of summary characteristics of neonates with candidemia by survival status.

	Overall (n=127)	**Survived** (n=99)	**Died** (n=28)
Sex; Female (%)	59 (47)	44 (44)	15 (54)
Birth weight (g) (median [IQR])	1270.0 [990.0, 1692.5]	1300.00 [1022.5, 1724.5]	955.00 [772.0, 1655.0]
Gestational age (weeks) (median [IQR])	30 [28, 34]	30 [28, 34]	29 [27, 33]
Age at *Candida* spp. culture (days) (median [IQR])	16 [10.5, 22.0]	16.0 [12.0, 22.0]	14.5 [8.0, 22.5]
Birth status			
Hospitalised since birth (%)	114 (90)	90 (91)	24 (86)
Organism (n=128) (%)			
Candida albicans	45 (35)	35 (35)	10 (36)
Candida parapsilosis	38 (30)	31 (31)	7 (25)
Candida auris	18 (14)	13 (13)	5 (18)
Other *Candida* spp.[a]	27 (21)	21 (21)	6 (21)
Country (%)			
India	40 (32)	30 (30)	10 (36)
South Africa	55 (43)	44 (44)	11 (39)
Vietnam	13 (10)	10 (10)	3 (11)
Other[b]	19 (15)	15 (15)	4 (14)
Hospital (%)			
Hospital 1	28 (22)	22 (22)	6 (21)
Hospital 2	25 (20)	20 (20)	5 (18)
Hospital 3	21 (17)	17 (17)	4 (14)
Hospital 4	13 (10)	10 (10)	3 (11)
Hospital 5	11 (9)	8 (8)	3 (11)
Other[c]	29 (23)	22 (22)	7 (25)

[a]Other *Candida* spp. includes*: Candida famata (n=1), Candida glabrata (n=6), Candida metapsilosis (n=1), Candida pelliculosa (n=4), Candida rugosa (n=1), undefined Candida spp. (n=10), Candida tropicalis (n=4)*

[b]*Other countries is comprised of 5 countries, each contributing <8 participants (range: 1-7 per country).*

[c]*Other sites is comprised of 9 hospitals, each contributing <7 participants (range: 1-6 per site)*

Table 2. Univariable hazard ratios from Cox proportional hazards analysis. Significant covariates are bolded.

Mortality		**N (%)**	**Univariable hazard ratio (95%CI, p)**
Birthweight (1000g)	**≥ 1000g**	**95 (72.5)**	**-**
	<1000g	**36 (27.5)**	**3.83 (1.84-7.97, p<0.001)**
Gestational age	**≥28 weeks**	**104 (79.4)**	**-**
	<28 weeks	**27 (20.6)**	**2.32 (1.08-4.99, p=0.032)**
Organism	*Candida albicans*	48 (36.6)	-
	Candida parapsilosis	38 (29.0)	0.84 (0.32-2.16, p=0.711)
	Candida auris	18 (13.7)	1.28 (0.44-3.70, p=0.645)
	Other Candida spp.	27 (20.6)	0.92 (0.34-2.48, p=0.868)
Country	Country 1	40 (30.5)	-
	Country 2	55 (42.0)	0.82 (0.35-1.94, p=0.658)
	Country 3	13 (9.9)	0.77 (0.21-2.78, p=0.685)
	Other*	23 (17.6)	0.80 (0.27-2.34, p=0.681)
Hospital	Hospital 1	28 (21.4)	-
	Hospital 2	25 (19.1)	0.98 (0.30-3.22, p=0.977)
	Hospital 3	21 (16.0)	1.10 (0.31-3.91, p=0.883)
	Hospital 4	13 (9.9)	0.92 (0.23-3.70, p=0.911)
	Hospital 5	11 (8.4)	1.16 (0.29-4.63, p=0.837)
	Other*	33 (25.2)	1.11 (0.38-3.20, p=0.851)
Enrolment Cohort	Cohort 1	69 (52.7)	-
	Cohort 2	62 (47.3)	0.60 (0.29-1.27, p=0.186)