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Epidemiology, risk factors and outcomes associated with candidaemia in very low birth weight infants at a tertiary South African Hospital over a 7-year period (2013–2019)

Tanusha D. Ramdin [a,*], Vindana Chibabhai [b], Robin T. Saggers [a], Rossella M. Bandini [c], Daynia E. Ballot [c]

[a] Neonatal Unit, Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital and School of Clinical Medicine, University of the Witwatersrand, South Africa
[b] Department of Clinical Microbiology and Infectious Diseases, National Health Laboratory Service (NHLS), School of Pathology, University of the Witwatersrand, South Africa
[c] Project for Improving Neonatal Care (PRINCE), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, South Africa

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ABSTRACT

Introduction: Candidaemia is a significant problem in neonatal units and is associated with high morbidity, including long-term neurodevelopmental impairment in survivors, and high mortality of very low birth weight infants (VLBWI).

Method: A retrospective cohort study amongst VLBWI admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg, South Africa, from 1 January 2013 to 31 December 2019. All VLBWI were born at the hospital or transferred to the neonatal unit from birth to day 28 of life with blood culture confirmed candidaemia.

Results: During the study period, 3414 VLBWI were admitted to the unit. Of these, 5.12% (n = 176) developed culture confirmed candidaemia. The incidence was 5.1 per 1000 admissions. The most common species, which persisted throughout the study period, was *Candida parapsilosis*, followed by *Candida albicans*. *C. parapsilosis* peaked in 2018 while *C. albicans* peaked in 2015. Emergence of *C. auris* occurred in 2019. Important risk factors associated with the development of candidaemia included necrotizing enterocolitis ($p < 0.001$, OR 4.63 [3.29–6.54]), surgery ($p < 0.001$ OR 7.02 [4.48–11.12]), conventional ventilation ($p < 0.001$, OR 6.23 [4.48–8.68]), patent ductus arteriosus ($p < 0.001$, OR 3.81 [2.67–5.44]), intraventricular haemorrhage ($p < 0.001$, OR 3.32 [2.99–5.44]) and prolonged hospital stay ($p < 0.001$). Mortality was not statistically different ($p = 0.80$ OR 0.95[0.68–1.31]) between the two groups.

Conclusion: There is a high incidence of candidaemia in the neonatal unit. Several modifiable risk factors including improved antifungal stewardship and prevention of candidaemia with oral or systemic antifungal prophylaxis may decrease the incidence of candidaemia, and associated morbidity.

1. Background

Candidaemia is a significant problem in neonatal units and is associated with high morbidity, including long-term neurodevelopmental impairment in survivors, and high mortality of very low birth weight infants (VLBWI).[1–3] Globally, the mortality rate of candidaemia can be as high as 50%.[2,4–6] In a study conducted in our centre in 2013, the mortality rate from candidaemia was recorded at 45.8%.[3] Candidaemia is an important cause of late onset sepsis (LOS) in VLBWI and accounts for approximately 12% of all LOS.[7]

An early and reliable diagnosis of candidaemia is challenging. This is related to its nonspecific clinical presentation (lethargy, glycaemic instability, increased oxygen requirements, and thrombocytopenia) and the poor sensitivity of *Candida* isolation in culture, all of which may result in a delayed initiation of appropriate therapy.[1,3,8] In addition to

* Corresponding author. Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital, University of Witwatersrand, 7 York Road, Parktown, 2193, Johannesburg, South Africa.
E-mail addresses: tanusha.ramdin@wits.ac.za (T.D. Ramdin), vindana.chibabhai@nhls.ac.za (V. Chibabhai), robin.saggers@wits.ac.za (R.T. Saggers), rossella.bandini@wits.ac.za (R.M. Bandini), daynia.ballot@wits.ac.za (D.E. Ballot).

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Abbreviations

AFS	antifungal stewardship
AMS	antimicrobial stewardship
AFST	antifungal susceptibility testing
BDG	Beta-D-glucan
BC	blood culture
BPD	bronchopulmonary hypoplasia
CDC	Centre of Disease Control
CI	confidence interval
CLSI	Clinical and Laboratory Standard Institute
IDSA	Infectious Disease Society of America
HICS	high income country setting
IQR	interquartile range
IVH	intraventricular haemorrhage
LMICs	low middle income country setting
LOS	late-onset sepsis
MV	mechanical ventilation
NCPAP	nasal continuous positive airway pressure
NEC	necrotizing enterocolitis
OR	odds ratio
PDA	patent ductus aterious
PN	parenteral nutrition
REDCap	Research Electronic Data Capture
VLBWI	very low birth weight infants

blood stream infection with *Candida*, infants may develop meningitis, urinary tract infection, ophthalmitis and endocarditis.[9] A high index of suspicion and the use of investigations including retinal examination, echocardiography, and abdominal ultrasonography, may be necessary to confirm the suspected diagnosis. Serum 1, 3 beta-D glucan (BDG), a rapid, non-culture-based broad fungal antigen assay, has assisted in the early initiation of antifungal therapy in at-risk patients. Its use, followed by close follow-up and discontinuation of antifungal therapy when invasive candidiasis is excluded, has shown to improve outcomes of patients.[8,10,11]

VLBWI have a compromised immune system and mucosal integrity. Gastrointestinal tract colonization by *Candida* species, especially heavy colonization, may become a primary source of translocation through epithelial barriers and systemic dissemination in high-risk VLBWI.[2] The high morbidity and mortality associated with candidaemia in VLBWI render prevention of this infection essential.

Clinical implementation of antifungal stewardship (AFS) is recommended for acute-care hospitals.[12] A multidisciplinary team including a clinical microbiologist is required to implement and monitor AFS interventions. Audits of candidaemia and antifungal therapy should be performed in every neonatal unit.

Due to the paucity of data from the neonatal population, and specifically from the African continent, this study was undertaken to determine the change in the prevalence and epidemiology of candidaemia in our setting as well as to describe the associated risk factors and mortality in VLBWI with candidaemia.

2. Methods

2.1. Study design

We performed a retrospective cohort study amongst VLBWI admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg, South Africa, from 1 January 2013 to 31 December 2019.

(Fungal sepsis in a small subset of this cohort was previously published).[7]

2.2. Study setting

Charlotte Maxeke Johannesburg Academic Hospital has a 90-bed high care and low care neonatal unit, including a 10-bed kangaroo mother care ward and a 14-bed combined paediatric and neonatal intensive care unit.

In this unit, infants suspected of nosocomial fungal infections are treated with empiric Amphotericin B deoxycholate therapy while awaiting blood culture and BDG results. Empiric antifungal therapy is based on unit-specific prevalence and antifungal susceptibility patterns of specific *Candida* species. A high prevalence of azole resistant non-albicans *Candida* species, including *C. parapsilosis,* in South Africa renders the routine use of empiric fluconazole inappropriate.[3,13]

2.3. Inclusion criteria

All VLBWI were born at the hospital or transferred to the neonatal unit from birth to day 28 of life.

2.4. Exclusion criteria

Infants with incomplete or missing information were excluded from the study.

2.5. Data collection

Data was managed using Research Electronic Data Capture (REDCap), hosted by the University of the Witwatersrand.[14] Maternal, labour room and neonatal variables were collected.

Definitions

Candidaemia:	At least one blood culture obtained by peripheral venipuncture which cultured *Candida* species.
Necrotizing enterocolitis:	Modified Bell's criteria of stage 2 or more[15]
Intraventricular Haemorrhage:	diagnosed on cranial ultrasound and defined using Papiles's score of grade 3 and grade 4[16]
Early onset sepsis:	blood culture proven sepsis <72 h of life
Late onset sepsis:	blood culture proven sepsis >72 h of life
Delivery room resuscitation:	bag mask ventilation or CPR and adrenaline after delivery
Bronchopulmonary dysplasia:	requiring oxygen >28 days of life

2.6. Microbiologic methods

Blood cultures requested for fungal culture were incubated in the BacTAlert® automated blood culture system for 14 days. Once the bottle flagged positive, the bottle was removed, a Gram stain was performed, and the results thereof reported immediately to the attending clinician. Bottles with yeasts visible on Gram stain were plated out onto 5% sheep blood agar, chocolate agar, and Sabouraud dextrose agar. These were incubated at 37 °C for 72 h.

Once yeast isolates were cultured, they were identified using the Vitek® MS MALDI-TOF (Matrix-assisted Laser Desorption Ionisation –

Time of Flight) analyzer or the Vitek® 2 automated identification and antimicrobial susceptibility testing system. Antifungal susceptibility test (AFST) results were obtained using the Vitek® 2 or the gradient diffusion method for species where no clinical interpretive breakpoints were available. AFSTS were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. *Candida auris* isolates were interpreted using the tentative Centers for Disease Control and Prevention (CDC) breakpoint.

2.7. Statistical analysis

Statistical analysis was performed using SPSS version 27 (IBM, USA). Continuous data with normal distribution were described using mean and standard deviation, and skewed data were described using median and interquartile range (IQR). Categorical data were described using frequencies and percentages. VLBWI with candidaemia were compared to VLBWI without candidaemia. Potential risk factors associated with candidemia were identified using logistic regression analysis. Variables with 2-tailed *P*-value <0.05 were defined as statistically significant. Odds ratios (ORs) along with 95% confidence intervals (CIs) were used to assess the strength of any association.

2.8. Ethical considerations

Permission to perform this study was granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M180625).

3. Results

During the study period, 3414 VLBWI were admitted to the unit of these, 5.12% (n = 176) developed cultures confirmed candidaemia. The incidence was 5.1 per 1000 admissions.

The most common species, which persisted throughout the study period, was *Candida parapsilosis*, followed by *Candida albicans* (see Fig. 1.) *C. parapsilosis* peaked in 2018 while *C. albicans* peaked in 2015. Emergence of *C. auris* occurred in 2019. The data from 2013 to 2014 had missing species names (n = 84; 34.15%); hence, these were omitted in Fig. 1.

The total percentages for 5-year period (excluding 2013 and 2014) were 60.49% for C. *parapsilosis*, 28.40% for C. *albicans*, 6.17% for other *Candida* species, 3.09% for C.*auris,* and 1.85% for C. *glabarata.*

Birth weight, gestational age and length of hospital stay associated with candidaemia are shown in Table 1.

The maternal and neonatal factors associated with candidemia in VLBWI are summarized in Table 2 and Table 3.

The univariate analysis of clinical factors and fungal sepsis in Tables 1 and 2 found many of the variables to be statistically significant, namely, necrotizing enterocolitis (NEC), surgery, parenteral nutrition (PN), conventional ventilation, nasal continuous positive airway pressure (NCPAP) ventilation, patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH), late onset sepsis, bronchopulmonary dysplasia (BPD) and prolonged hospital stay.

Mortality was not statistically significant (p = 0.80 OR 0.95[0.68–1.31]) between the two groups.

4. Discussion

There has been a significant increase in the incidence of candidaemia in VLBWI in our neonatal unit. In 2013 the incidence was 1.2 per 1 000 admissions, 2014 it was 1.5 per 1 000 admissions and 5.1 per 1 000 admissions in 2019.[3,7] However, this is based on an imperfect gold standard because blood cultures lack sensitivity for fungal sepsis.[10,17] The incidence of candidaemia was comparable to other studies in low and middle income countries (LMICs), but significantly higher than studies conducted in high income countries (HICS).[2,3,12] This is likely related to overcrowding, poor infection control measures and inappropriate antibiotic use in the neonatal unit.

During the study period, our neonatal unit observed a change from a predominance of *C. albicans* to *C. parapsilosis* candidaemia and the emergence of *C. auris* in 2019.[3] This is consistent with national surveillance data which has seen a rise in *C. auris* since 2014.[12,18,19] Globally,*C. auris* now accounts for one in 10 cases of candidemia.[20] This presents a very serious global health threat. This emphasises the importance of C. *auris* identification on blood culture and screening of patients when transmission or colonization of *C. auris* is suspected to prevent and control the spread in neonatal units. *C. auris* is difficult to eradicate in the neonatal unit and is resistant to treat. Similarly, to a study by V. Chibabhai, our study, further highlights the high prevalence of azole resistant C. *parapsilosis* and C.*auris* due to prior exposure to broad spectrum antibiotics[13] The Federation of Infectious Diseases Societies of Southern Africa has recently published guidelines pertaining to the detection, management, and prevention of healthcare-associated *C. auris* infection.[20]

Factors such as the presence of central venous catheters and endotracheal tubes, ventilation, delayed enteral feeding, necrotizing

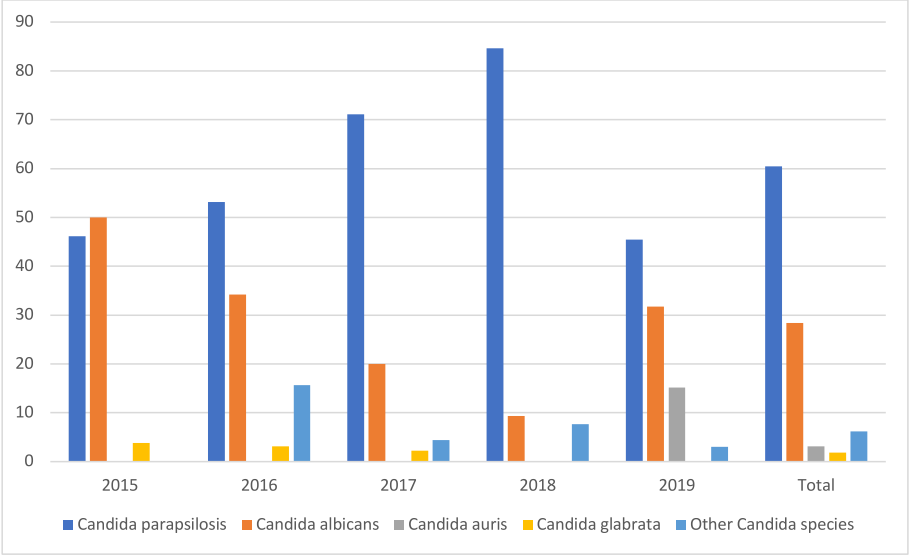

Fig. 1. Annual percentage distribution of Candidaemia episodes according to the 5 most common isolated Candida species.

Table 1
Continuous variables associated with candidaemia in VLBWI at a tertiary hospital in Johannesburg, South Africa.

Variable	Category	Fungal sepsis		P-value	Odds Ratio (95%CI)
		No N (%)	Yes N (%)		
Birth weight (g)	Median (IQR)	1130 (920–1310)	1050 (910–1230)	**0.01**	1.00(0.99–1.00)
Gestational age (weeks)	Mean (SD)	29.00 (2.65)	28.49 (2.27)	**<0.001**	**0.85(0.77–0.94)**
Length of hospital stay (days)	Median (IQR)	25 (9–43)	50 (26–72)	**<0.001**	**1.03(1.02–1.03)**

Table 2
Maternal variables associated with candidemia in VLBWI at a tertiary hospital in Johannesburg, South Africa.

Variable	Category	Fungal sepsis		P-value*	Odds Ratio (95%CI)
		No N (%)	Yes N (%)		
Maternal HIV status	Positive	942 (29.2)	60 (34.3)	0.09	1.26 (0.92–1.74)
N = 3399	Negative	2 281 (70.8)	116 (65.7)		
Mode of delivery	Vaginal	1 342 (43.2)	68 (44.7)	0.38	0.94 (0.68–1.30)
N = 3236	Caesarean section	1 742 (56.8)	84 (54.1)		
Antenatal care	Yes	2 399 (79.4)	118 (76.6)	0.42	0.85 (0.58–1.25)
N = 3175	No	622 (20.6)	36 (23.5)		
Antenatal steroids	Yes	1 376 (49.0)	73 (52.1)	0.49	1.13 (0.81–1.59)
N = 2946	No	1 430 (51.0)	67 (47.9)		
Chorioamnionitis	Yes	85 (2.8)	9 (5.1)	0.06	1.99 (0.99–4.03)
N = 3383	No	3 123 (97.4)	166 (94.9)		

Table 3
Neonatal variables associated with candidemia in VLBWI at a tertiary hospital in Johannesburg, South Africa.

Variable	Category	Fungal sepsis			Odds Ratio (95%CI)
		No N (%)	Yes N (%)		
Place of birth	Outborn	628 (18.4)	57 (32.6)	**<0.001**	2.01 (1.45–2.79)
N = 3414	Inborn	2 611 (80.6)	118 (67.4)		
Initial resuscitation in the delivery room	Yes	2 186 (69,0)	115 (68.0)	0.87	0.96 (0.69–1.34
N = 3338	No	983 (31.0)	54 (32.0)		
Necrotising enterocolitis	Yes	2 921 (91.1)	119 (68.8)	**<0.001**	**4.64 (3.30–6.54)**
N = 3380	No	286 (8.9)	54 (31.2)		
Other surgery	Yes	84 (2.8)	28 (16.8)	**<0.001**	**7.02 (4.43–11.12)**
N = 3177	No	2 926 (97.2)	139 (83.2)		
Parenteral nutrition	Yes	105 (20.3)	15 (48.9)	**<0.001**	**3.46 (1.67–7.14)**
N = 548	No	411 (79.7)	17 (53.1)		
Patent ductus arteriosus	Yes	287 (8.89)	47 (27.2)	**<0.001**	**3.81 (2.67–5.44)**
N = 3394	No	2 932 (91.1)	128 (72.8)		
Intraventricular haemorrhage	No	3 091 (95.4)	151 (86.3)	**<0.001**	**3.319 (2.09–5.27)**
N = 3414	Yes	148 (4.6)	24 (13.7)		
Conventional Ventilation	No	2 263 (75.7)	56 (33.3)	**<0.001**	**6.23 (4.48–8.68)**
N = 3157	Yes	726 (24.3)	112 (66.7)		
NCPAP ventilation	Yes	2 108 (69.5)	139 (84.3)	**<0.001**	**2.44 (1.58–3.76)**
N = 3197	No	925 (30.5)	25 (15.2)		
Early onset of bacterial sepsis	No	3 077 (95.5)	170 (97.1)	0.34	0.62 (0.25–1.54)
N = 3398	Yes	145 (4.5)	6 (2.9)		
Late onset of bacterial sepsis	No	2 327 (72.3)	0	**<0.001**	**0.27 (0.26–0.29)**
N = 3393	Yes	891 (27.7)	175 (100)		
Breastfeeding method	Breast & formula	113 (5.6)	7 (7.1)	**0.02**	**2.85 (2.05–3.96)**
N = 2103	Breastmilk only	971 (48.5)	34 (34.3)		
	Formula only	920 (45.9	58 (58.6)		
Death outcome	No	2 260 (69.8)	120 (68.6)	0.80	0.95 (0.68–1.31)
N = 3405	Yes	970 (30.2)	55 (31.4)		

*Chi-^{2}.
p-values for categorical variables.

enterocolitis and surgery increase fungal colonization and candidaemia.[2,7] Prolonged use of parenteral nutrition (PN) and the use of certain medications, such as broad-spectrum antibiotics, corticosteroids, histamine type 2-receptor blockers, and theophylline, also increase the risk of candidaemia.[2,21] Similarly,in our study risk factors identified included NEC, surgery, PN, ventilation, LOS, PDA, IVH and BPD. However, this suggests critically ill VLBWI were more susceptible to candidaemia as well as prolonged hospital admission. These risk factors could be incorporated in a Candida score to implement early initiation of antifungal treatment in neonatal units to decrease morbidity and mortality.[22]

In the current study, mortality was not significantly different in the two groups. However, the unit has a high rate of bacterial LOS and other complications of prematurity, which contributes to the overall high mortality rate in the nonfungal sepsis group of this study cohort.

Based on the findings of our study, we recommend that Amphotericin B continue to be used as empiric therapy based on the predominance of non-albicans *Candida* species in VLBWI presenting with suspected LOS and risk factors including NEC, surgery, PN. Babies with evidence of PDA, IVH, and those with prolonged hospital stay should also be considered for empiric therapy when LOS is suspected. There is little evidence that echinocandins penetrate the blood-brain barrier and should be used with caution in neonates or avoided, since meningoencephalitis cannot easily be identified and excluded on lumbar punctures.[23]

Using AFS principles, antifungal therapy should be started empirically only in critically ill VLBWIs with thrombocytopenia after collection of blood cultures including fungal blood cultures and BDG or other non-culture based diagnostic assays (depending on availability). In cases where the blood culture is negative for *Candida* species, the BDG is not suggestive, and an alternative diagnosis is found, the antifungal agent

should be discontinued. When azole susceptible species have been identified, de-escalation of azoles is recommended once repeat blood cultures are confirmed to be negative and adequate source control obtained.[17,24]

The Infectious Diseases Society of America (IDSA) guidelines recommend antifungal prophylaxis in neonatal units with fungal sepsis incidence rates >10%.[24] This should be considered in settings with high-risk neonates. A recent Cochrane review concluded that prophylactic systemic antifungal therapy reduces the incidence of invasive fungal infection in VLBWI.[8] However, the results should be interpreted cautiously due to the high incidence of invasive fungal infection in the control groups of many of the included trials. Additionally, there was no statistically significant decrease in mortality and there is only limited data on the long-term neurodevelopmental consequences for infants exposed to this intervention.[1,8] The emergence of antifungal resistance remains an important concern when using prophylactic antifungal therapy.[3,8]

In settings with high rates of non-albicans candidaemia, oral nystatin prophylaxis is easily available, affordable, and easily administered.

4.1. Limitations

Our study has several limitations. This was a retrospective study with some missing data. There was a difference in data collection methodology before 2015, meaning species were not recorded. Missing species data in 2013 and 2014 may have skewed the species distribution. The study was based on blood culture positive cases only. Fungal sepsis diagnosed using non-culture-based techniques such as BDG and clinical suspicion were not included and may be the reason for the lower prevalence documented in this study. This was a single-centre study, and the findings may not be broadly applicable in other settings.

5. Conclusion

The study found that there is a high incidence risk of candidaemia within the neonatal unit. Significant risk factors for candidaemia included NEC, surgery, mechanical ventilation, and prolonged hospital stay. In 2019, there was an emergence of *C auris*. Several modifiable factors including improved antifungal stewardship and prevention of candidaemia with oral or systemic antifungal prophylaxis may decrease the mortality from candidaemia.

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Declaration of competing interest

None.

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