Invasive fungal infections in a paediatric intensive care unit in a low-to middle-income country

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Background. Paediatric intensive care units (PICUs) are high-risk settings for healthcare-associated infections. Invasive fungal infection (IFI) is one of the common causes of healthcare-associated infections.

Objective. To describe the prevalence and short-term outcomes of children with IFI, and to offer a basis for the efficient prevention and treatment of IFI.

Methods. A retrospective study was conducted in children under the age of 12 years over a two-year period. Participants were categorised according to pre-defined microbiology criteria into IFI if they had a positive culture from blood or other sterile sites. Data collected included demographics, invasive procedures, length of stay and mortality.

Results. One thousand and forty-two children were admitted during the study period. Of the total, 56.8% ($n = 592$) were male. Median length of stay was 18 days (mean ± SE 18.6±8.9). IFI was identified in 35 cases per 1 000 admissions, with 77.7% of these infants under the age of one year. The mean length of stay was 18.6 days compared with 7.5 days for children with bacterial infections. The in-hospital mortality for invasive fungal infection was 36% compared with 16% for all admissions. Findings confirmed that colonisation was more prevalent than IFI.

Conclusion. IFIs are common among infants, and these patients have a higher mortality rate and prolonged hospital stay. Therefore we recommend early diagnosis and timely treatment with high-performance antifungal drugs to improve the prognosis in children with IFI.

Keywords. Healthcare-associated infections, South Africa, neonates, mortality, sepsis.

Most paediatric intensive care units (PICUs) in low- to middle-income countries (LMICs) are multidisciplinary, admitting both medical and surgical patients. The innate vulnerability of critically ill children and the invasive nature of their care make the PICU a high-risk setting for healthcare-associated infections (HAIs). HAIs are potentially preventable conditions that, when acquired, are a significant cause of morbidity and mortality. A mortality rate of ~15% in both high-income (HIC) and LMIC settings[1-3] has been recorded. A multi-national study on the prevalence of HAIs in children in Europe found the highest rates in PICUs (15.5%) and neonatal intensive care units (10.7%), followed by neonatology wards (3.5%), paediatric surgery wards (3.4%) and general paediatric wards (1.8%).[1] The overall mortality attributed to paediatric HAIs has been estimated at 11%, with invasive fungal infections (IFIs) being among the top four causes of paediatric HAI.[4] In the United State of America, data from the National Nosocomial Infections Surveillance System found an incidence of nosocomial fungal infections of 3.8 per 1 000 PICU survivors.[5]

Two South African (SA) studies reported a HAI prevalence of 16.5% and 15.3%, respectively.[2,3] Within the fungal infections, candidiasis is reported to be the most common infection, being responsible for between 40% and 60% of fungal infections.[4,5] *Candida* species are the most common cause of nosocomial fungal bloodstream infections, accounting for between 8% and 15% of infections.[5] Fungal infections are associated with increased length of stay, mortality and escalation of costs.[5-7] The risk of bloodstream infection (BSI) due to non-albicans *Candida* species has been independently associated with duration of central venous catheter (CVC) use and proportion of days of fluconazole exposure.[8]

Risk factors identified for nosocomial fungal infection include use of broad-spectrum antibiotics, use of invasive procedures such as central venous and urinary catheters, parenteral nutrition, pre-existing bacterial infection, immune-compromised status, recent surgery, dialysis,

mechanical ventilation, age less than 12 months and prolonged length of stay.[1,6] Colonisation often precedes infection. GIT colonisation with *Candida* species is a significant risk factor for invasive candidiasis, with the risk increasing with an increase in the number of sites colonised.[9,10]

Invasive fungal infections are associated with an overall mortality of 11%.[4] A critical factor associated with this high mortality is delay in institution of appropriate anti-fungal treatment.[5] The present study was conducted to describe the incidence of IFI and short-term outcomes of children with invasive fungal infections admitted to a PICU in a LMIC.

Materials and methods
Study participants and setting
A retrospective cohort study was conducted at the 14-bed PICU at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, KwaZulu-Natal (KZN), SA, during the two-year period between 1 January 2015 and 31 December 2016. This centre is one of three public sector paediatric intensive care units in the province of KZN and serves a childhood population of over three million. IALCH provides tertiary and quaternary services to the entire KZN province and part of the Eastern Cape. The unit serves medical and surgical needs of critically ill children aged 0 - 12 years and admits 500 - 550 children annually (2010 - 2014).

Study variables
Dependent variable
- Mortality

Independent variables
- Socio-demographic factors (age, gender and date of birth)
- Clinical: diagnosis and organ systems affected, length of stay (date of admission to date of discharge/death)
- Laboratory: human immunodeficiency virus (HIV) status, serum beta-D-Glucan levels, microbiology (blood, urine, endotracheal aspirates, fluids). HIV polymerase chain reaction (PCR) using Ampliprep cabas/taqman for HIV-1 qualitative testing version 2.0 was used to determine the HIV status of children less than 18 months of age at admission and HIV enzyme-linked immunosorbent assay (ELISA) using Abbott architect/Roche cobas e601, for children more than 18 months of age.
- Interventions: catheters (central venous catheter, urinary catheter and endotracheal tubes), parenteral nutrition, surgery during admission and antimicrobial usage.

Eligibility criteria
Inclusion criteria: All children admitted to the unit during the study period were included in the study, and they were classified according to pre-specified study criteria related to microbiology results. The IFIs were classified as those patients with positive culture from the blood or sterile sites (intra-operational specimen). Probable fungal infection were those patients with fungal isolates from both urine and endotracheal samples with evidence of elevated markers of sepsis. The isolates from either urine or endotracheal samples and without associated markers of sepsis were regarded as contaminants or colonisers.

Ethical consideration
Prior to data collection, an official written letter from the first author was submitted to the ethical committee. Honesty and confidentiality were maintained throughout. Ethical approval was granted by the University of KZN Biomedical Research Ethical Committee, reference BE640/16.

Data processing and analysis
Data were entered, cleaned and checked using Excel spreadsheet and analysed using the Statistical Package for Social Sciences software version 27.0 (SPSS Corp., USA). Categorical variables were summarised as numbers and percentages, whereas normally distributed continuous data was presented as means and standard deviations by descriptive statistics. Finally, the result was presented by means of tables.

Results
Patients' characteristics
A total of 1 042 patients were admitted during the study period. Fifty percent of admissions were due to respiratory problems, 32% to GIT and 9% each to cardiac and haematology problems. Of the 1 042 admissions, 36 had IFI, with an incidence of 35 per 1 000 admissions. Eighty-one percent of the invasive fungal infections were nosocomial infections, meaning that cultures were done more than 48 hours after admission. Beta-D-Glucan was done on a few patients; low Beta-D-Glucan levels do not rule out fungal infection. The highest proportion of patients was less than one year old. Most of the participants were male 592 (56.8%), while the proportion of those who were of black ethnicity was 985 (94.5%). Also, findings revealed that the proportion of HIV-negative patients (79.7%) was higher than those who were HIV-positive (9.6%) while ~11% patients did not specify their HIV status (Table 1).

Microbiological outcome findings among children admitted to the paediatric ICU
The analysis of the microbiological specimens collected from the children revealed a variety of culture results. Based on the analysis, findings confirmed that endotracheal tube aspirate (ETA) and urine were the higher proportion among all the fungal cultures compared with blood culture (BC). More details are shown in Table 2.

Clinical outcome of children with invasive fungal infections
In total, 36 patients had IFI, of which the majority were males (56.3%) and 28 (77.7%) were under the age of 1 year (Table 3). All children had received prior antibiotic therapy and had urinary catheterisation, whilst 97.2% had invasive ventilation with endotracheal tubes. Two-thirds (63.4%) had central catheters in place and almost half (44.4%) had previous surgery. The mean length of stay in ICU among those with invasive fungal infections was 18.6 ±8.9 days while the mean length of stay for children who had only bacterial infections in the same study period was of 7.3 days, with the actual mean difference of 11 days. The overall in-hospital mortality rate for all admissions was 16% (*n*=170/1 042) and it was higher for those with IFI at 36.1% (*n*=13/36).

Mortality description with type of *Candida* species among children in PICU

Candida was the predominant fungal pathogen identified in the PICU during the study period, with *C. albicans* being the predominant *Candida* species in over a third of cases (36.1%) (Table 4). Of the 36 species in samples, the most common were *C.* non-speciated (*n*=16), *C. albicans* (*n*=13), and *C. parapsilosis* (*n*=4), respectively. Twenty-one percent of all patents admitted to ICU had positive fungal cultures during their PICU stay, with only 16.4% of those being IFIs and the rest classified as probable infection or colonisation.

Discussion

In the present study, *Candida* was the only fungus isolated from patients admitted to the PICU. A small but significant proportion of children had IFIs while the remainder were probable infection or colonisers. Of those with IFIs, the majority were infants under the age of one year and they had all previously been exposed to antibiotics and urinary catheterisation. Children with IFIs had higher mortality compared with those with probable infections or colonisers.

Opportunistic fungal infections that cause diseases in immunocompromised individuals, e.g. aspergillosis and zygomycosis, were not detected in this population. The incidence of IFIs was 35 per 1 000 admissions, which was higher than the 3.5 cases per 1 000 PICU admissions reported in the USA in 2000.[6,11] There was also a higher colonisation rate with *Candida*, with the higher the number of sites with *Candida* colonisation, the higher the likelihood of invasive *Candida*.[12] Monitoring for colonisation with *Candida* species in children undergoing treatment for severe sepsis or septic shock

Table 1. Demographic and clinical characteristics of patients at presentation (*N*=1 042)

Variables	*n* (%)
Race	
Black	985 (94.5)
Asian	30 (2.9)
Coloured	12 (1.2)
White	6 (0.6)
Unspecified	9 (0.9)
Age (years)	
<1	663 (63.6)
≥1<5	234 (22.5)
≥5<10	84 (8.1)
≥10	41 (3.9)
Unspecified	20 (1.9)
Gender	
Male	592 (56.8)
Female	450 (43.2)
HIV status	
Negative	830 (79.7)
Positive	100 (9.6)
Unspecified	112 (10.7)
Mortality	165 (15.8)
Beta-D-Glucan	
≥80	74 (7.1)
<80	75 (7.2)
Not done	893 (85.7)

Table 3. Characteristics and outcome of children with IFIs (*N*=36)

Variables	IFI (*n*/%)
Length of stay (days) mean (SD) 18.6±8.9	
Age	
<28 days	12 (33.3)
1 month - 1 year	16 (44.4)
1 - 5 years	6 (16.7)
5 - 12 years	2 (5.6)
Sex	
Male	20 (55.6)
Female	16 (44.4)
Invasive device	
Central venous catheter	23 (63.4)
Urinary catheter	36 (100)
Endotracheal tube	35 (97.2)
Parenteral nutrition	17 (47.2)
Surgery	16 (44.4)
Antibiotics	36 (100)
Mortality	13 (36)

Table 4. Spectrum of *Candida* species in children in PICU

Species	*n* (%)
C. albicans	13 (36.1)
C. parapsilosis	4 (11.1)
C. sake	1 (2.8)
C. tropicalis	2 (5.6)
C. non-speciated	16 (44.4)
Total	36

C = *Candida*.

Table 2. Microbiological findings among all 1 042 children admitted to paediatric ICU

Cultures	BC (*n*/%)	ETA (*n*/%)	UMCS (*n*/%)	CSF (*n*/%)	Fluid (*n*/%)	Total
Bacteria	88 (8.4)	267(25.6)	56 (5.4)	8 (0.8)	56 (5.4)	475
Fungal	25 (2.4)	104 (10.0)	86 (8.3)	0 (0.0)	4 (0.4)	219
Multiple	6 (0.6)	47 (4.5)	7 (0.7)	0 (0.0)	6 (0.6)	66
Negative*	890 (85.4)	497 (47.7)	767 (73.6)	62 (6.0)	15 (1.4)	2 219
Not done†	33 (3.2)	127 (12.2)	126 (12.1)	972 (93.3)	961 (92.2)	

BC = blood culture; ETA = endotracheal aspirate; UMCS = urine microscopy culture and sensitivity; CSF = cerebrovascular fluid.
*Negative (no organisms detected).
†Not done (no cultures done).

in PICU for more than five days may offer an opportunity for early intervention to prevent candidaemia.[13]

Reported risk factors for fungal infection include central venous catheters and arterial lines, parenteral nutrition, mechanical ventilation, malignancy and extended use of antimicrobials that enhance the risk of IFI.[14] Previously identified independent predictors of candidaemia were presence of colonisation and Paediatric Risk of Mortality score.[12,13] We did not include the Paediatric Risk of Mortality score in the current study; this study found that all children with IFIs had at least two risk factors for infections, in line with previous studies.

C. albicans accounted for 36.1% of all invasive isolates, which was comparable with reports of *C. albicans* being the most prevalent isolate in other studies.[12,14] *C. albicans* remains the leading cause of invasive *candida* in the PICU, but an increasing trend of non-albicans *Candida* spp has been reported worldwide.[15] *C. glabrata* is more prevalent in surgical patients or those with a central venous line; *C. tropicalis* is more common among patients with malignant disease or neutropenia; and *C. parapsilosis* is frequently seen among infants or those on parenteral nutrition.[7]

The crude mortality for IFI of 36.1% was higher than overall in-hospital mortality rates of 16.3% during the study period. This figure is not dissimilar to the 30-day mortality rate of patients with candidaemia of 26% seen in other studies although we did not look at this outcome in our cohort.[16] Also contributing to the high IFI case-fatality rate in our cohort was the young age. Mortality rates as high as 50% have been seen in extremely low-birthweight neonates with IFI.[15] In our study, 30.8% (4/13) of those who died were neonates. In addition, the increased length of stay for those with IFIs as compared with children co-admitted with bacterial infections could be associated with higher morbidity and mortality in this group. This increased length of hospital stay would increase cost of care and limit PICU access for other critically ill patients.

Early appropriate therapy of IFI is imperative although the role of empiric antifungals remains controversial. The use of beta-D-Glucan in the paediatric population could assist in early diagnosis, even though it is not diagnostic, but persistently high levels are suggestive of fungal infection and it may improve outcomes with therapy. However, the low beta-D-Glucan does not exclude fungal infection. Prophylactic and empiric antifungal therapy has been associated with the development of resistance. New antifungal agents are required for the emerging challenges related to resistant fungal infections.

Some limitations with the current data are its retrospective nature and the small number of IFIs. In addition, the present study did not review the immune status of the patients and therefore could not stratify cases according to immunological risk. The lack of equivalent non-fungal-infected comparative groups makes interpretation of the findings challenging. The major strength of the study was the ability to quantify the burden of fungal infections in a PICU. The identification of patients with risk factors for IFI to begin a search for fungal infections and to initiate empiric antifungal therapy is important. Adjustment of therapy according to microbiological confirmation is essential as prolonged duration is a risk factor for IFI.

In conclusion, IFIs are more common in young infants with indwelling invasive devices. These infections have associated increased mortality and length of PICU stay. Early diagnosis and treatment of IFI

should be beneficial in improving these and consequently increasing access to the limited PICU resources. High rates of colonisation or probable infection require further evaluation.

Recommendations

A similar study will benefit from having predictive mortality scores included. A case-control study in this unit comparing IFI with the control is recommended. A degree of immunosuppression for future studies needs to be included and analysed to assess impact on the outcome.

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