Invasive Candidiasis in pediatric patients at King Fahad Medical City in Central Saudi Arabia

A 5-year retrospective study

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ABSTRACT

الأهداف: تحديد العوامل المهيئة للمرض، وتوزيع الأنواع، وقابلية الفطريات، والنتيجة.

الطريقة: أجريت هذه المراجعة بأثر رجعي في مستشفى للأطفال بمدينة الملك فهد الطبية. تم قبول 129 طفل مع داء المبيضات الغازية من يناير 2010م إلى يناير 2015م.

النتائج: وقد أظهرت نتائج التحليل الإحصائي مجموعة من عوامل الخطر 37 (28.7%) من المرضى، وانخفاض الوزن عند الولادة في 42 (32.6%)، القسطرة الوريدية المركزية في 59 (45.7%)، الخبيثة في 21 (16.3%)، العلاج المناعي في 20 (15.5%)، دعم التنفس الصناعي 60 (46.5%). وكان معدّل الوفيات أكثر من مرتين في المرضى الذين لديهم ناميات في القلب (OR: 2.9) والمرضى الذين كان المبيضات معزولة عن دمهم أكثر من مرتين من المرجح أن يموت كما المرضى الذين يعانون من المبيضات معزولة عن مواقع أخرى (OR: 2.2). توفي ما مجموعه 48.3% من المرضى على جهاز التنفس الصناعي مقابل 26.1% الذين لم يكونوا على جهاز التنفس الصناعي (p=0.009)؛ و 3.8% من المرضى في وحدة العناية المركزة توفي مقابل 24.5% فقط من المرضى الذين لم يكونوا في وحدة العناية المركزة C . (p=0.03). أظهرت بارابيلوسيس أعلى معدل وفيات (56.2%).

الخاتمة: البيكانز هو العزلة الأكثر شيوعاً بين جميع أنواع المبيضات. الجنس، وانخفاض الوزن عند الولادة، وإقامة وحدة العناية المركزة لفترات طويلة، وجود الناميات، مزرعة الدم الإيجابية والتهوية الميكانيكية كعوامل خطر تنبؤية قوية للوفاة لدى الأطفال الذين يعانون من داء المبيضات الغازية، وهي النتيجة التي يمكن تطبيقها كمؤشر وقائي في الأطفال المصابين بأمراض خطيرة وخاصة المواليد.

Objectives: To identify predisposing factors, species distribution, antifungal susceptibility, and outcome.

Methods: This study is a retrospective chart review that was conducted at a children's hospital at King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia. One hundred twenty-nine children with invasive candidiasis who were admitted between January 2010 and January 2015.

Results: The statistical analysis results have revealed a group of risk factors; prematurity in 37 (28.7%) of patients, low birth weight in 42 (32.6%), central venous catheter in 59 (45.7%), malignancy in 21 (16.3%), immunotherapy in 20 (15.5%), and ventilator support in 60 (46.5%). More than 2-fold mortality rate in patients who had heart vegetation (odds ratio [OR]: 2.9) and patients who had Candida isolated from their blood were more than twice as likely to die as patients with Candida isolated from other sites (OR: 2.2). A total of 48.3% of patients on ventilator died versus 26.1% who were not on ventilator (*p*=0.009); and 43.8% of patients in the ICU died versus only 24.5% of patients who were not in the ICU (*p*=0.03). *Candida parapsilosis* exhibited the highest mortality rate (56.2%).

Conclusion: *Candida albicans* is the most common isolate among all Candida species. Gender, low birth weight, prolonged ICU stay, presence of vegetation, positive blood culture, and mechanical ventilation as a strong predictive risk factors for death in children with invasive candidiasis, a finding that could be applied as prophylactic indicator in critically ill children especially neonates.

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Candida species are the most common cause of invasive fungal infections in humans; Candida is considered the fourth most common isolate and is associated with the second highest case fatality rate in children with bloodstream infections. The manifestations of infection can range from non-life-threatening mucocutaneous disorders to an invasive disease that can involve any organ.[1] The most frequently affected organs in children with disseminated candidiasis are the lungs, liver, kidney, and brain. The frequency of invasive candidiasis is greater in children than in adults and is particularly high in neonates.[2] The most frequently implicated risk factors include the use of broad-spectrum antibacterial agents, the use of central venous catheters, the receipt of parenteral nutrition, the receipt of renal replacement therapy, neutropenia, malignancy, the use of implantable prosthetic devices, and the receipt of immunosuppressive agents.[3] *Candida albicans* (*C. albicans*) is the most common invasive *Candida spp.* in pediatric patients, accounting for 53% of cases. *Candida parapsilosis* (21%) and *Candida tropicalis* (10%) are the most prevalent *non-C. albicans spp.*, whereas *Candida glabrata* (*C. glabrata*) and *Candida krusei* (*C. krusei)* are infrequent.[4] The Prospective Antifungal Therapy Alliance (PATH Alliance) registry describes the epidemiology and outcomes of invasive candidiasis caused by non-albicans species from 2004 to 2008, which accounted for more than 50% of all cases of invasive candidiasis.[5] Currently, most Candida treatment guidelines recommend early empiric antifungal therapy for patients suspected or known to have an invasive Candida infection, pending confirmation of the species and its antimicrobial susceptibilities.[6-11] The late introduction of appropriate antifungal therapy is an important contributor to the high morbidity and mortality associated with invasive Candida infections that has been reported in several studies.[12-16] The mortality rate that is attributable to invasive candidiasis is approximately 86% among intensive care unit (ICU) patients and 42% among non-ICU patients.[5] The assessment of these risk factors and the development of a valid risk score are important for early interventions with appropriate antifungal therapy and can reduce the burden of infection.

The objectives of our study are to acquire baseline demographic data, to identify the risk factors for the development of invasive Candida infection, and to review the antifungal susceptibility testing for different Candida species as well as to assess the clinical outcome of invasive candidiasis in pediatric patients at King Fahad Medical City (KFMC), Riyadh, Kingdom of Saudi Arabia to provide important comparative data. Prospective multi-center studies regarding pediatric invasive candidiasis have been conducted in specific regions of the world,[17-19] but additional research is needed to fill important knowledge gaps in pediatric candidiasis.

Methods. This study is a retrospective chart review that was conducted at a children's hospital at KFMC. King Fahad Medical City is a referral hospital with 250 beds of all subspecialties allocated for children. The proposal for this study was approved by the institutional review board of the KFMC, Riyadh, KSA. All pediatric patients from birth until 14 years of age based on the study proposal inclusion criteria, who were diagnosed with invasive candidiasis were recruited. Invasive candidiasis was defined as the isolation of Candida from blood, cerebrospinal fluid (CSF), or other sterile body fluids such as synovial fluid, peritoneal fluid and pleural fluid. All patients were treated in our hospital from January 2010 to January 2015. We excluded patients in whom Candida had been isolated from tissues and urine. A sample of 129 was identified: 114 from blood, 7 from cerebral spinal fluid, and 8 from other sterile body fluids. A data collection form composed of 7 sections and 51 question items was designed to gather information for this study. All necessary variables were collected and statistically analyzed. Obtained demographic and clinical data from the charts includes; age, gender, nationality, and underlying disease. Risk factors included prematurity, low birth weight, trauma, neutropenia, total parenteral nutrition, steroids, and presence of a central venous catheter, underlying gastrointestinal disease, recent surgery, recent broad-spectrum antibiotic treatment, antifungal therapy, and admission to an ICU. Each data sheet had a code.

Microbiology. Specimen processing. A minimum sample of 3 milliliters of blood was collected in pediatric blood vials and inoculated in a BACTEC instrument (Becton Dickinson) until it was determined to be positive by the machine. Gram stains were performed for all positive cultures, and samples were subcultured on blood, MacConkey, chocolate, and Sabouraud agar. Colonies on Sabouraud agar were identified as germ tube test positive for *Candida albicans*; other Candida species were identified using an API 20C AUX (bioMérieux, Paris, France). Antifungal susceptibility testing was performed on Mueller-Hinton agar with 2% glucose.

Minimal inhibitory concentrations were determined with an E-test using a breakpoint reference from the Clinical and Laboratory Standards Institute (CLSI M27-S4) to determine the antifungal susceptibility of yeasts.[20]

Data management. A well-designed, consensually validated data collection form was applied to gather data for this study. It was composed of 7 sections that included 51 items. Study members collected the data. Data were then initially entered into Excel and cross-checked by the data management team members to identify missing values and anomalies before finally transferring the data to the statistical software.

Statistical analysis. Data were analyzed with the Statistical Analysis Software SAS V9.4. (SAS institute, NC, USA), and a *p*-value of ≤0.05 was accepted as the significance level for all statistical tests. All collected variables were analyzed using descriptive and inferential statistics. Categorical variables were described and reported as counts and percentages. Continuous variables were described and reported as means±standard deviation. Patient survival status was the main study outcome variable and was analyzed versus all demographic and clinical characteristics of patients via univariate and multivariate analyses.

Results. The majority of patients (n=123 [95.4%]) were Saudi, and almost 67 (51.9%) were males, with a mean age of 2.4±1.41 years. The reported risk factors were found to be: prematurity in 37 (28.7%) patients, low birth weight in 42 (32.6%) patients, the presence of a central venous catheter in 59 (45.7%) patients, malignancy in 21 (16.3%) patients, immunotherapy in 20 (15.5%) patients, and the required use of mechanical ventilators in 60 (46.5%) patients (**Table 1**). Among patients with Candida infections, *C. albicans* was isolated from 59 (45.7%) patients, *C. tropicalis* isolated from 28 (21.7%) patients, *C. parapsilosis* isolated from 16 (12.4%) patients, *Candida famata* from 7 (5.4%) patients, *Candida lusitaniae* from 5 (3.9%) patients, and other species were isolated from 14 (10.9%) patients (**Table 2**). The univariate analysis identified gender, ventilator use, low birth weight, presence of echocardiography vegetation, and intensive care as significant risk factors for poor prognosis and death in children with invasive candidiasis. The results revealed that 46.8% of females and 26.9% of males died (*p*=0.02). The mortality rate of patients on ventilator support was 48.3%, versus 26.1% on patients not on ventilator (*p*=0.009). The mortality rate of patients who stayed in the ICU was 43.8% versus 24.5% in

Table 1 - Sociodemographic and clinical characteristics of 129 patients with invasive candidiasis who were admitted in King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia, between January 2010 and January 2015.

Characteristics	n (%)
Nationality	
Saudi	123 (95.4)
Non-Saudi	6 (4.6)
Gender	
Males	67 (51.9)
Females	62 (48.1)
Premature	
Yes	37 (28.7)
No	92 (71.3)
Low birth weight	
Yes	42 (32.6)
No	87 (67.4)
Dialysis	
Yes	11 (8.5)
No	118 (91.5)
Neutropenia	
Yes	24 (18.6)
No	105 (81.4)
Malignancy	
Yes	21 (16.3)
No	108 (83.7)
Antibiotics	
Yes	85 (65.9)
Underwent surgery	31 (36.5)
With malignancy	15 (17.7)
No	44 (34.1)
Previous anti fungal	
Yes	32 (24.8)
No	97 (75.2)
Recent steroid	
Yes	19 (14.7)
No	110 (85.3)
Surgery	
Yes	41 (31.8)
No	88 (68.2)
Central venous catheter (CVC)	
Yes	59 (45.7)
No	70 (54.3)
Cardiovascular Case Reports	
Peripherally inserted central catheter	6 (4.7)
Permanent	25 (19.4)
Temporary	13 (10.1)
No CVC	85 (56.9)
No	49 (38.0)
Arterial catheter	
Yes	6 (4.7)
No	123 (95.4)
Immunotherapy	
Yes	20 (15.5)
No	109 (84.5)
Immunodeficiency	
Yes	13 (10.1)
No	116 (89.9)
Total parenteral nutrition	
Yes	45 (34.9)
No	84 (65.1)
Ventilation	
Yes	60 (46.5)
No	69 (53.5)
Intensive care unit stay	
Yes	80 (62.0)
No	49 (38.0)

patients who did not stay in the ICU (*p*=0.03) (**Table 3**). Multivariate analysis revealed that the mortality rate in patients with cardiac vegetation was increased almost 3 times (OR: 2.9) (**Table 4**). In the same time, death was noticed increased by more than 2-fold in patients with Candida isolated from their blood, those with low birth weight, those on ventilator, and those with prolonged ICU stay compared to others (**Table 4**). *Candida parapsilosis* was found to have the highest mortality rate among all Candida species (56.2%), predominantly in neonates (**Table 6**).

Discussion. Our review included 129 pediatric patients with invasive candidiasis from a tertiary medical center representing the largest series in the pediatric age group in Saudi Arabia. The study has investigated the mortality rate and identified the predictive risk factors in the study group. We found that gender, prolonged ICU stay, blood candidemia and ventilation support were the major risk factors for invasive candidiasis and associated with high mortality rate. Coexistence of multiple risk factors in females and in patients with *C. parapsilosis* have increased the mortality rates within these subgroups.

Candida species are a major contributor to morbidity and mortality in hospitalized children. Data from the National Healthcare Safety Network have identified *Candida spp.* as the second most common cause, behind coagulase negative staphylococci, of central line-associated bloodstream infection in hospitalized patients in the US.[21] Among hospitalized children, fungi are the second most common pathogen identified in the setting of sepsis[22,23] and are the leading infectious

cause of death in children with cancer[24,25] or following an organ or hematopoietic stem cell transplant.[26,27] The all-cause mortality associated with pediatric candidiasis exceeds 15%, with an attributable mortality of 10%.[28] Prospective multi-center studies have been conducted to examine pediatric invasive candidiasis in specific regions of the world,[17–19] but additional research is

Table 3 - Univariate analysis of patient characteristics versus survival status (n=129).

Characteristics	Survived	Died	*P*-value
Gender			
Males	49 (73.1)	18 (26.9)	0.0192
Females	33 (53.2)	29 (46.8)	
Ventilation			
Yes	31 (51.7)	29 (48.3)	0.0091
No	51 (73.9)	18 (26.1)	
ICU stay			
Yes	45 (56.3)	35 (43.8)	0.0274
No	37 (75.5)	12 (24.5)	
Low birth weight			
Yes	15 (35.7)	27 (64.3)	0.0001
No	67 (77.0)	20 (23.0)	
Prematurity			
Yes	13 (35.1)	24 (64.7)	0.0001
No	69 (75.0)	23 (25.0)	
Site of Candida (site isolated)			
Blood	50 (61.7)	31 (38.3)	0.5732
Other sites	32 (66.7)	16 (33.3)	
ECHO results			
Presence of vegetation	12 (42.9)	16 (57.1)	0.0278
No vegetation	70 (69.3)	31 (30.7)	
Catheter			
Removed	80 (63.0)	47 (29.1)	0.2814
Not removed	2 (100.0)	0	

Data are expressed as number and percentage (%).
ECHO - echocardiography

Table 2 - Clinical and laboratory characteristics of Candida (n=129) age 2.4±1.41 years.

Characteristics	Total children	Infant	Neonate
Species			
Candida albicans	59 (45.7)	30 (50.9)	29 (49.1)
Candida tropicalis	28 (21.7)	17 (60.7)	11 (39.3)
Candida parapsilosis	16 (12.4)	5 (31.3)	11 (68.8)
Candida famata	7 (5.4)	4 (57.1)	3 (42.9)
Candida lusitaniae	5 (3.9)	1 (20.0)	4 (80.0)
Other candida	14 (10.9)	6 (42.9)	8 (57.1)
Site			
Blood	114 (88.4)		
Peritoneal fluid	5 (3.9)		
Pleural fluid	2 (1.6)		
Cerebrospinal fluid	7 (5.4)		
Synovial fluid	1 (0.8)		
Clinical outcome			
Full recovery	51 (39.5)		
Recovery with sequelae	31 (24.0)		
Death	47 (36.4)		

Data are expressed as number and percentage (%)

Table 4 - Multivariate analysis of patient characteristics versus survival status (n=129).

Characteristics	Odds ratio	95% confidence interval	*P*-value
Gender			
Males versus females	0.3	(0.07 - 1.46)	0.14
Prematurity			
Premature versus normal	1.0	(0.21 - 5.12)	0.96
Birth weigh			
Low versus normal birth weight	2.2	(0.42 - 11.57)	0.35
Ventilator			
Yes versus no	2.4	(0.45 - 12.96)	0.30
Intensive care unit stay			
Yes versus no	2.4	(0.29 - 19.75)	0.42
ECHO vegetation			
Yes versus no	2.9	(0.66 - 12.57)	0.16
Site of Candida			
Blood versus other sites	2.2	(0.71 - 6.93)	0.17

ECHO - echocardiography

Table 5 - Antifungal susceptibility of Candida species (n=129).

Isolate	Caspofungin			Voriconazole			Fluconazole			Ampicillin		
	S	I	R	S	I	R	S	I	R	S	I	R
Candida albicans	52	0	1	54	0	3	49	4	5	36	1	0
Candida tropicalis	26	1	0	23	3	1	19	2	6	21	0	0
Candida parapsilosis	10	0	2	15	1	0	13	2	1	11	0	1
Other species	15	0	0	10	5	0	10	3	2	12	0	0
Total	103	1	3	102	9	4	91	11	14	80	1	1

The sum is not 129 (assay were not performed for all samples). S - sensitive, I - intermediate, R - resistant

Table 6 - Mortality by Candida species (n=129).

Type	Total	Outcome		
		Full recovery	Recovery with sequelae	Death
Candida albicans	59	21	15	23
Candida tropicalis	28	14	6	8
Candida parapsilosis	16	4	3	9
Other candida species	26	12	7	7
Total	129	51	31	47

Table 7 - Mortality by site of blood culture (n=129).

Site of culture	Total	Outcome		
		Full recovery	Recovery with sequelae	Death
Blood	114	45	25	44
Cerebrospinal fluid	7	4	3	0
Peritoneal fluid	5	1	2	2
Pleural fluid	2	1	1	0
Synovial fluid	1	0	0	1
Total	129	51	31	47

needed to fill important knowledge gaps in pediatric candidiasis.

While aspects of pediatric and adult invasive candidiasis are similar, numerous studies have revealed critical differences in host factors, pharmacokinetics, and outcomes in children that underscore the importance of dedicated pediatric studies.[28-33] Candidiasis disproportionately affects critically ill children. In 2000, approximately 50% of the candidemia cases in children in the US occurred in patients in an ICU setting.[28] Moreover, Candidiasis among ICU patients is associated with higher mortality rates.[33,34] In 2010, Zaoutis et al[35] derived a clinical prediction rule for candidemia among pediatric ICU patients. The single center model determined that the presence of a central venous catheter, recent exposure to certain antimicrobial agents (vancomycin, anti-anaerobic agents), recent exposure to parenteral nutrition, and underlying malignancy resulted in a predictive probability for candidemia of 46% (95% CI: 19%-75%).

Candida albicans (48.3%) was the most common species, but collectively the non-albicans Candida species predominated (51.6%) (**Table 2**), which is comparable to the results of the largest multi-center, multi-national study of pediatric candidiasis, in which a total of 441 episodes of invasive candidiasis were identified in 423 patients from 30 participating sites (20 in the US and 10 international).[36] Of the 449 Candida isolates recovered from the 441 episodes, *C. albicans* (40%) was the most common species, but collectively the non-albicans

Candida species predominated (60%). Similarly, the largest and most contemporary retrospective review from a single pediatric center (patients aged 6 months to 18 years old) found that *C. albicans* was the most common isolate (44.2%), followed by *C. parapsilosis* (23.9%).[37] The only difference between our study and the previously mentioned studies, as well as other studies, is that *C. tropicalis* was the second most common Candida species that was identified in patients with invasive candidiasis. Nevertheless, we stress the importance of separately analyzing pediatric and neonatal patients in future studies, as well as the need for multinational collaboration for a more accurate description of species distribution.

This study showed that most non-albicans species included *C. tropicalis* (23%) and *C. parapsilosis* (13.1%). *Candida famata* (5.7%) was more common in our study than *C. lusitaniae* (4.1%) and *C. glabrata* (2.5%) (**Table 2**). Interestingly, none of the previous local studies have addressed this issue. A study by Omrani et al[38] conducted in the same region showed the following distribution: *C. albicans* was the most common species (38.7%), followed by *C. tropicalis* (18.9%), and *C. glabrata* (16.3%).

This study revealed good in vitro susceptibility rates of Candida species to the available antifungal medication in our medical city; 78% of isolates were susceptible to fluconazole, 88.7% were susceptible to voriconazole, 96.3% were susceptible to caspofungin, and 97.6% were susceptible to amphotericin B (**Table 5**).

This susceptibility pattern in our institution is similar to that described in a review by Omrani et al,[38] which reported good susceptibility patterns to all antifungal medications.

Our study assessed the clinical prognostic outcome of invasive candidiasis in the Kingdom of Saudi Arabia. The overall mortality in this study is considered low compared to those in local, regional, and international reports, and mortality was calculated at the end of therapy. A similar study of predictors and outcomes of Candida infection of the bloodstream in the region reported a mortality rate of 50%,[2] while another international study of Candida infections reported a high crude mortality of 46-75%, which reflected the severe underlying illnesses of the infected patients.[5]

In conclusion, pediatric candidiasis continues to change with respect to its epidemiology and risk factors in specific patient populations. In general, invasive candidiasis in the Kingdom of Saudi Arabia has a poor clinical prognostic outcome. This study has revealed significant proportion of death within females, patients with candida isolated from blood, those on ventilators and those with prolonged ICU stay as well. One of the limitations is the retrospective nature of the study and the dependence on one site data. However, the findings highlighted the common predictors that may guide early prophylactic intervention and the need for further prospective studies. Only through detailed multi-center studies will the medical community be able to best define the risks and optimal strategies for early diagnosis

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