Evaluation of Candida colonization and use of the Candida Colonization Index in a paediatric Intensive Care Unit: a prospective observational study

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SUMMARY

Invasive candidiasis is an important cause of morbidity and mortality, which primarily occurs in intensive care units. The *Candida* colonization index is an accepted score as an early warning tool for invasive candidiasis. This study was performed in a medical PICU with patients prone to contracting invasive candidiasis, to determine the usefulness of the *Candida* colonization index in forecasting invasive candidiasis in children. This prospective study including 87 patients (children 1 month to 16 years old with several illnesses and requiring ICU care) was conducted in a 22-bed medical PICU, Health Science University of Kayseri Training and Research Hospital, between January 2015 and September 2016. Those patients not on antifungal therapy, who were expected to stay more than seven days in PICU and had no history of a PICU stay within the previous two months were included in the study. In all patients, rectal, cervical, throat, axillary, perineal and nasal swab cultures, urine culture and blood culture tests were performed at admission and every week throughout their stay. Overall, 2639 swab and urine cultures (mean: 30.3) and 325 blood cultures (mean: 3.73) were obtained from 87 patients and a total of 576 grew *Candida* spp. In patients' swab and urine cultures *C. albicans* was detected in 64.5%, *C. parapsilosis* in 12.1%, *C. glabrata* in 7.5%, *Saccharomyces* spp in 3.0 %, *C. tropicalis* in 2.4%, *C. krusei* in 2.1% and *C. kefyr* in 1.2%. Three patients had *C. albicans* and one had *C. parapsilosis* growth in blood culture. Sensitivity, specificity, positive predictive value and negative predictive value for CI were found to be 33.73%, 100%, 6.7%, and 100%, respectively.
Patients are at risk of fungal infection in paediatric intensive care units. Specificity and the negative predictive value of 100 % indicate that CI is a useful score to rule out the presence of invasive fungal disease. On the other hand, the low rate of sensitivity (33.3%) and positive predictive value (6,7%) make this score less reliable in forecasting invasive candidiasis in children.

Keywords: pediatric intensive care, candida, candida colonization index, candidiasis.

INTRODUCTION

Invasive candidiasis is an important cause of morbidity and mortality, which usually occurs in intensive care units (ICUs). Candidemia is the most common form of invasive candidiasis. It is the third leading cause of bloodstream infections whereas it is the second leading cause of sepsis-related mortality in children [1-3]. Although candidemia is the most common form of invasive candidiasis, the diagnosis is rare and often overlooked due to the prevention of growth with empirical antifungal agents initiated in ICUs and the presence of infection by *Candida* spp. such as *C. glabrata* whose growth in culture is challenging or requires prolonged incubation period for growth [4]. Early empirical treatment of severe candidia-

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sis has improved survival but is responsible for the overuse of antifungals and this leads to increase financial cost and more resistant Candida isolates [5].

Previous studies have shown that *Candida* spp. can neither be eradicated nor prevented as readily as many bacterial pathogens when they grew in blood culture tests; rather, *Candida* infections cause a form of sepsis which results in death in most cases. Given that *Candida* infections have a highly fatal course among patients treated in ICUs, it is necessary to establish an alarm system against such pathogens in which early diagnosis and treatment cannot be achieved and for the early detection of patients likely to benefit from early antifungal treatment.

The risk factors have been identified in patients with candidemia and efforts have been made to develop and implement several scores for the most common species [6-8]. *Candida* colonization index (CI) is one of the most widely accepted scores. Studies on this score have been focused on adult patients and certain group of diseases in general. We aimed to show the feasibility of this score by using it in pediatric patients with no pre-defined specific disease group (such as malignancy or immunodeficiency) who are at high risk for invasive candidiasis in pediatric intensive care units (PICUs) and to contribute to *Candida* epidemiology by reporting demographic data from our PICU.

PATIENTS AND METHODS

This prospective study including 87 patients was conducted in a 22-bed PICU (including 10 Level II and 11 Level III PICU beds) between January 2015 and September 2016. Our unit is a medical PICU - including those other than special patient groups (such as oncologic or surgical) - serving patients aged 1 month to 16 years who have several illnesses and require ICU care. Patients not on antifungal therapy, who were expected to stay more than 7 days in ICU and had no history of ICU stay within the previous 2 months were included in the study. Patients with neutropenia and those with positive *Candida* cultures within the previous 2 months were excluded.

The study was approved by the Ethics Committee of Erciyes University Medicine School. Written informed consent was obtained from parents. In all patients, data sheets were used to record age, gender, diagnosis, PRISM (Pediatric Risk of Mortality) score, underlying diseases, colonization risk factors, laboratory findings at admission and during follow-up, and length of ICU stay. Total parenteral nutrition, steroid or immunosuppressive use, presence of bacterial infection, antibiotic use and duration, invasive procedures (mechanical ventilation, central catheterization, urinary catheter, and drains), trauma, surgery, blood transfusion, hemodialysis/peritoneal dialysis and co-morbid conditions were recorded as risk factors.

In all patients, from the body parts more prone to have fungi colonization according the previous studies; rectal, cervical, throat, axillary, perineal and nasal swab cultures; urine culture and blood cultures were performed at admission and every week throughout their stay [5, 7, 9]. Swab samples were obtained by using swab sticks while urine samples were collected as mid-stream urine or from a urinary catheter, if present. Blood samples were also obtained from a central venous catheter if present while tracheal aspirate was used in patients with mechanical ventilation. Blood culture was obtained in all patients at admission to ICU and repeated in the presence of two or more systemic inflammatory response criteria [10]. The Candida Colonization index was calculated for each patient.

Mycological assessment

Samples were inoculated onto Sabouraud dextrose agar containing penicillin (20 U/mL) and chloramphenicol (16 µg/mL). Cultures were examined at hours 24 and 48 after incubation at 37°C. Yeast isolates were identified by using the germ tube test, cycloheximide susceptibility, nitrate reduction test, urea hydrolysis, carbohydrate assimilation test (API 20C AUX; bioMérieux, France) and appearance on chromogenic agar (Oxoid, UK).

Strains isolated from blood were examined by the microdilution method for amphotericin B, fluconazole, voriconazole, and itraconazole susceptibility; and by gradient test (AB Biodisk, Sweden) for caspofungin susceptibility. The RPMI media containing 2% glucose and 1.5% agar was used in this method and susceptibility was tested in accordance with CLSI M27-A3 and M27S recommendations [11].

Candida colonization index

The *Candida* colonization index (CI) was calculated as the proportion of the number of distinct body sites (other than blood culture) colonized with *Candida* spp. over the total number of sites cultured. Colonization was considered as mild when CI>0.2 whereas it was considered high when CI≥0.5 [2].

Statistical analysis

Data distribution was analyzed by using histogram, q-q plots and the Shapiro-Wilk test. Quantitative variables were compared by using the Mann Whitney U test. Categorical variables were compared by using Pearson χ^2 analysis. Data were analyzed by R Studio 3.2.2 (r-project.org). A p value<0.05 was considered to be statistically significant.

RESULTS

Eighty-seven children from PICU were enrolled in the study, including 40 girls and 47 boys. The mean age was 35.7 months (1-194 months).

Overall, 2639 swab and urine cultures (mean: 30.3) and 325 blood cultures (mean: 3.73) were obtained from 87 patients.

At least one yeast growth was detected in 71 patients (81.7%) while no yeast growth was detected in the remaining 16 patients (18.3%). Yeast growth was detected in 329 (13.7%) of 2401 urine and swab samples collected from 71 patients.

Of the patients with yeast growth in any of samples obtained, 34 (47%) were girls whereas 37 (53%) were boys, indicating no significant difference regarding gender (p=0.158). The mean age was 66.64±17.75 (18-91 months) and 64.29±17.46 (18-93) months in patients with and without yeast growth, respectively. No significant difference was found in age between groups (p=0.511).

Overall, 325 blood culture tests were performed. Of these, yeast growth was detected in 9 blood cultures from 4 patients. *C. albicans* growth was detected in 3 patients whereas *C. parapsilosis* was detected in one patient. Two patients were considered as having invasive candidiasis as growth was detected in both blood and catheter cultures while other two patients were considered only candidemia.

Yeast growth was most common in rectal, perineal and throat samples. *C. albicans* in 64.5%, *C. parapsilosis* in 12.1%, *C. glabrata* in 7.5%, *Saccharomyces* in 3.0%, *C. tropicalis* in 2.4%, *C. krusei* in 2.1% and *C. kefyr* in 1.2% (Table 1).

Of 71 patients with yeast growth, the CI was found to be >0.2 in 59 patients (67.8%) whereas it was ≥0.5 in 29 patients (33.3%). The sensitivity, specificity, positive predictive value and negative predictive value for CI were found to be 33.73%, 100%, 6.7% and 100%, respectively in reference to candidemia.

It was observed that colonization occurred most intensely at weeks 2 and 3 after PICU admission. Table 2 presents the demographic data of patients according to the CI. It was found that there was a significant relationship between the CI and urinary catheterization when CI threshold was defined as >0.2 (p<0.028) whereas there was a significant relationship between the CI and length of stay when the CI threshold was defined as ≥0.5 (p<0.030). In patients with *Candida* colonization, no significant relationship was found between

Table 1 - Distribution of yeast species according to clinical samples.

Genus	*Rectal*	*Perineum*	*Throat*	*Nose*	*Urine*	*Neck*	*Axilla*	*Blood*	*Total (%)*
C. albicans	45	37	38	29	26	19	18	3	215 (64.5)
C. parapsilosis	8	6	7	8	5	5	1	1	41 (12.1)
C. glabrata	7	4	4	2	3	2	3	0	25 (7.5)
Saccharomyces spp.	3	2	2	1	0	1	1	0	10 (3)
C. tropicalis	1	1	3	2	0	1	0	0	8 (2.4)
C. krusei	3	2	0	0	2	0	0	0	7(2.1)
C. kefyr	1	0	1	1	0	1	0	0	4 (1.2)

*Multiple grown yeasts: *C. albicans/C. glabrata, C. albicans/C. parapsilosis, C. albicans/C. tropicalis, C. albicans/C. krusei, C. albicans/C. kefyr, C. albicans/Saccharomyces, C. albicans/C. glabrata/C. kefyr, C. albicans/C. glabrata/C. parasilosis/C. kefyr, C. albicans/C. glabrata/C. parapsilosis/C. krusei*

Table 2 - Demographic data of patients.

	Colonization index groups					
Variables	*CI≤0.2*	*CI>0,2*	*p*	*CI<0,5*	*CI≥0.5*	*p*
Age	11.0(2.5-34.5)	10.0(4.8-44.0)	0.349	12.0(4.0-51.0)	9.0(4.0-24.8)	0.085
Gender *Male* *Female*	 15(51.7) 14(48.3)	 32(55.2) 26(44.8)	0.939	 31(52.5) 28(47.5)	 16(57.1) 12(42.9)	0.863
PRISM	6.0(2.5-13.0)	9.5(4.0-21.0)	0.088	6.0(3.0-16.0)	11.5(6.5-20.5)	0.635
Duration of stay in PICU	14.0(7.0-33.5)	23.5(11.8-43.0)	0.018	15.0(8.0-37.0)	29.0(19.0-54.5)	0.030
Total number of cultures	7.0(7.0-35.0)	21.0(14.0-49.0)	0.011	14.0(7.0-35.0)	28(21.0-54.3)	0.007
Total number of grown culture	0.0(0.0-1.0)	7.0(4.0-12.0)	<0.001	2.0(0.0-5.0)	11(9.0-18.5)	<0.001
Risk factors						
Mechanical ventilation	19(65.5)	49(84.5)	0.081	43(72.9)	25(89.3)	0.146
CV catheter	11(37.9)	24(41.4)	0.938	22(37.3)	13(46.4)	0.563
Urinary catheter	9(31.0)	34(58.6)	0.028	25(42.4)	18(64.3)	0.093
Dialysis	2(6.9)	3(5.2)	1.000	4(6.8)	1(3.6)	1.000
Blood transfusion	13(44.8)	31(53.4)	0.596	29(49.2)	15(53.6)	0.876
Bacterial Infection	15(51.7)	34(58.6)	0.702	33(55.9)	16(57.1)	1.000
Vancomycin use						
<14 days	22(43.1)	29(56,9)	0.021	40(78.4)	11(21.6)	0.021
≥14 days	7(19.4)	29(80.6)		19(52.0)	17(47.2)	
Meropenem days	7.18±10.76	11.32±11.66	0.176	8.03±12.41	13.92±15.20	0.580
Antifungal days	1.44±4.39	6.08±14.15	0.890	4.27±13.20	5.10±9.13	0.763
Total antibiotic days	3.72±1.98	4.58±1.98	0.059	4.11±1.98	4.67±2.05	0.227
Underlying diseases						
Hematologic	2(6.9)	8(13.8)	0.485	6(10.2)	4(14.3)	0.721
Neurologic	8(27.6)	19(32.8)	0.806	21(35.6)	6(21.4)	0.277
Cardiologic	6(20.7)	12(20.7)	1.000	11(18.6)	7(25.0)	0.689
Renal	0(0.0)	3(5.2)	0.548	1(1.7)	2(7.1)	0.241
Malignancy	4(13.8)	2(3.4)	0.092	5(8.5)	1(3.6)	0.659
Others	4(13.8)	4(6.9)	0.432	7(11.9)	1(3.6)	0.428
PrimaryDiagnosis						
Respiratory	12(41.4)	33(56.9)	0.255	32(54.2)	13(46.4)	0.652
GIS	4(13.8)	4(6.9)	0.432	6(10.2)	2(7.1)	1.000
Infectious-fever	4(13.8)	14(24.1)	0.400	12(20.3)	6(21.4)	1.000
Neurological	5(17.2)	14(24.1)	0.646	11(18.6)	8(28.6)	0.442
Surgery	2(6.9)	2(3.4)	0.598	3(5.1)	1(36)	1.000
Renal	2(6.9)	5(8.6)	1.000	4(6.8)	3(10.7)	0.676
Cardiovascular	8(27.6)	12(20.7)	0.652	10(16.9)	10(35.7)	0.095

CI: Colonization index, PRISM: Pediatric Risk of Mortality, PICU: Pediatric Intensive Care Unit, CV: central venous, GIS: Gastrointestinal system.

colonization and age, gender or risk factors. PRISM scores (mean: 13.2) were markedly higher in patients with high colonization; however, the difference did not reach statistical significance. The rate of mechanical ventilation was found to be higher in patients with mild colonization when compared to those without colonization, but the difference did not reach statistical significance.

It was not possible to assess antibiotic use as a risk factor since antibiotic therapy was initiated in all patients admitted to ICU and most of the patients were admitted to PICU directly, so the antibiotics used before PICU could not be analyzed as risk factors. However, the frequency and duration of antibiotic therapy were found to be significant in patients with CI>0.5 when vancomycin, meropenem, amikacin, third generation cephalosporins and their combinations were assessed ($p<0.001$).

In these PICU patients who were expected to have candidemia having risk factors of use of catheter, prolonged stay in PICU, and extended multi antibiotic use, antifungals were prescribed. As the study developed, the clinician was informed about the patients' CI and those patients were also prescribed antifungals. Depending on the patients' clinical appearance and biochemical parameters the antifungal agent differed from fluconazole to amphotericin B and caspofungin. The antifungal therapy approach did not have very absolute boundary in our PICU. Thirteen patients received fluconazole over 226 days while 13 patients received amphotericin B over 154 days in terms of sepsis or severe other infections to have the benefit of rapid effect of the drug and 2 patients received caspofungin over 15 days in total. No yeast growth was detected in the patient who received empirical antifungal therapy.

The longer the patient stayed in PICU the more he/she had cultures done. So, the more culture done the more yeast growth and colonization were recorded. Table 3 reveals the number of total cultures, grown cultures and length of stay in PICU according to CI scores. It has been found a statistically significant relationship between CI and length of stay in PICU.

When the mortality related to infection/colonization was assessed, it was found that the mortality rate was 12.5% among patients without colonization, 30.9% among those with varying degrees of colonization and 100% in patients with candidemia.

The mean time from admission to PICU to candidemia was 34.75 days. Yeasts growing in blood culture were found to be identical to yeasts colonizing urine and different areas.

In the antifungal susceptibility tests performed on *C. albicans* isolated from blood cultures, the MIC values were found to between 0.002-0.125 mcg/mL for amphotericin B whereas they were between 0.16-0.50 mcg/mL for fluconazole, 0.03-0.012 mcg/mL for voriconazole and itraconazole, 0.016-0.25 mcg/mL for caspofungin and 0.003-0.006 mcg/mL for anidulafungin. In the susceptibility tests on *C. parapsilosis*, the MIC values were found to be 0.125 mcg/mL for amphotericin B, 1.0 mcg/mL for fluconazole, 0.006 mcg/ml for voriconazole, 0.03 mcg/mL for itraconazole, 0.12 mcg/mL for caspofungin and 0.12 mcg/mL for anidulafungin.

DISCUSSION

Candida infection has become increasingly more prevalent in ICUs [12]. Invasive candidiasis, the most severe form of *Candida* infection, is an infection with varying incidences in ICUs, which displays a highly fatal course. Currently, colonization is an accepted risk factor for the development of invasive candidiasis [13]. The colonization rate may vary among studies and patient populations studied; however, it has been reported as 50-80% in adult patients, and 50-70% in pediatric patients [14-17]. In this study, the CI was found to be >0.2 in 67.8% (59/87) whereas it was >0.5 in 33.3%

Table 3 - Number of positive cultures according to the number of week stay in PICU calculated in different CI.

	CI≤0.2	*CI>0.2*	*p*	*CI≥0.5*	*CI>0.5*	*p*
Length of stay (day)	583	2091	<0.05	1456	1218	NS
Total cultures	567	2072	<0.05	1869	770	<0.05
Grown cultures	19 (3.3%)	554 (26 %)	<0.05	170 (9%)	403 (52 %)	<0.05

CI: Colonization index, PICU: Pediatric Intensive Care Unit.

(29/87) of the patients. Some studies reported that invasive candidiasis develops in 3-25% of the patients with *Candida* colonization [6,17,18]. In this study, invasive candidiasis occurred in 2 (2.6%; 2/87) of 4 patients with candidemia (4/87). Although the rate of invasive candidiasis appeared to be low, this may be due to the fact that the study was conducted in a PICU providing general medical care (excluding surgery, hematological disorders and malignancy etc.).

When patients with colonization were assessed in our study regardless of the CI>0.2 or CI>0.5, no significant difference was detected regarding age or gender but all patients with candidemia (n=4) were younger than one year of age. This may suggest that children aged younger than one year have a predisposition to invasive infection similar to elders. Likewise, an inverse proportion was found between colonization and gestational age in newborns [19].

In a study on PICU patients with candidemia, Hegazi et al. found that the PRISM score was >15 in 43.9% of patients, suggesting that a PRISM score >15 is a risk factor for mortality [20]. In a study on patients with severe sepsis, Singhi et al. found the median PRISM score as 9.5 and suggested that the PRISM score was a good marker for candidemia in patients staying in PICU for >5 days [6, 12, 16]. Although the PRISM score was found to be markedly high in patients with high colonization in our study, it was not possible to show that the PRISM score affected colonization which is similar to many adult studies investigating APACHE and PRISM scores [21].

In agreement with previous studies, no significant correlation was detected between colonization and underlying disease or cause for ICU admission (p>0.05) [1, 3, 5, 6, 18].

In an international, prospective multicenter study involving 33 medical and surgical ICUs from 3 different countries, Leon et al. found that length of hospital stay, and ICU stay were significantly longer in patients with *Candida* colonization and invasive candidiasis than in those without colonization (p<0.001) [3]. In case of prolonged stay in ICU, the invasive procedures performed, development of bacterial infections and antibiotic use, and attenuation in cutaneous and mucosal defense systems play a role as predisposing factors for *Candida* colonization [21]. In this study, there was a significant difference in the length of stay between patients with and without colonization which is in agreement with the literature possibly causing *Candida* colonization. This study revealed that urinary catheterization increases colonization; unfortunately, it is inevitably used in ICU patients.

It has been found that mechanical ventilation, central venous catheterization and broad-spectrum antibiotic use are associated with *Candida* colonization [1, 22-25]. It was emphasized that higher rates of parenteral nutrition may contribute to colonization and candidemia in an adult study by Pittet et al. and in a study in a pediatric population by MacDonald et al. [2, 26]. These factors lead to a loss of cutaneous and mucosal integrity which facilitates fungal colonization. In some studies on colonization, it was observed that the highest growth rates in rectal and perineal samples were associated with increased antibiotic use [6, 27]. Likewise, higher rates of yeast growth were also found in rectal, perineal and throat samples. This may indicate multiple antibiotic use.

In a retrospective study on 101 patients with candidemia, Zaoutis et al. emphasized that antibiotic use, particularly those with anaerobic coverage, will lead to *Candida* spp. colonization by suppressing anaerobic intestinal flora [28]. Vancomycin alone caused colonization in long-term use (>4 days), which was given to almost all patients [28]. In this study, vancomycin use (both 0-14 days or >14 days), the most commonly used antibiotic, was found to be significantly higher in patients with colonization (p<0.05). The total number of days of antibiotic use was also numerically higher in patients with colonization; however, the difference did not reach statistical significance (p=0.059). In the present study, fluconazole was the most commonly used antifungal; followed by amphotericin B. It is thought that empirical antifungal use could cause a lower rate of candidemia.

When *Candida* genus colonization was assessed, it was found that *C. albicans* was the most common pathogen (64.5%), followed by *C. parapsilosis* and *C. glabrata*. The colonized *Candida* species found throughout this study were also the most common causes of candidemia and invasive candidiasis, which has found to be in agreement with series investigating pediatric candidemia [3, 12, 28]. In a study investigating mortality rates in non-neutropenic patients with *Candida* coloniza-

tion, Leon et al. found that the mortality rate was 25.8% in ICU patients with single colonization or non-infected ICU patients whereas it was 31.9% in those with multiple colonization and 51.7% in patients with candidemia [8]. When the mortality rate was assessed according to the CI, no significant difference was found but mortality rates in our study were consistent especially in multiple colonized patients with the above-mentioned study. Zaoutis et al. reported that mortality rate was associated with *Candida* species and age in children with candidemia [28]. Wislinghoff et al. reported lower mortality rate as 19.6% than the present study for *Candida* species in bloodstream infection, making it the second leading cause of death after *Pseudomonas* spp. (28.7%). In the present study the number of patients with candidemia was too low so mortality rate might be relatively high. The authors also emphasized that approximately a half of all deaths were seen in patients aged <1 years [29]. Although the number of patients with candidemia was small, all fatal cases were younger than one year of age and causative agent was *C. albicans* in three quarters of these patients in this study, similar to the above studies.

Nosocomial candidemia is an important cause of infection in ICUs. It was reported that the rate of nosocomial candidemia was 6.9% in patients with colonization whereas it was 0.76% in those without colonization [30]. This rate may increase in studies on selected cases (hematological cancer, surgery or cancer). In a 3-year retrospective study conducted at the same PICU, the frequency of *Candida* spp. was found as 6.8% among all bloodstream infections [31]. Similarly, in a retrospective study in immunosuppressive children, Abelson et al. found candidemia frequency as 6.8% to 13.0% over the years [32]. In a study by Hegazi et al., candidemia frequency was found to be as high as 19% in a medical ICU [17]. In this study, candidemia was observed in 4.5% of patients. It is thought that the relatively lower rate in this study may be related to fact that this PICU usually admits patients with general medical problems rather than those with specific etiologies.

In agreement with the literature, the most common cause was *C. albicans*, followed by *C. parapsilosis* in cases with candidemia similar to colonization [32-34]. In cases with candidemia caused by *C. parapsilosis*, positive cultures were found in both blood and central venous catheter samples. In a study by Dotis et al. it was reported that *C. parapsilosis* grew more frequently in central venous catheters [35].

The positive predictive value of the CI was found to be low. Brissaud et al., explained this situation in medical ICU where a low incidence of candidemia was seen, although the CI is a useful tool, its positive predictive value maybe low [3].

In this study, isolates from patients with candidemia were found to be sensitive to all antifungal agents. In a study in 28 patients with candidemia, Kuzucu et al. found that all isolates were sensitive to amphotericin B while 5 isolates were resistant to itraconazole and 2 isolates were resistant to fluconazole [36]. In a 10-year study on pediatric candidemia by Trigiannidis et al., it was observed that yeasts (most were species other than *C. albicans*) were resistance to all antifungal agents, while flucanozole resistance was present in only one of the *C. albicans* isolates [36]. It is thought that no resistant isolate was observed in this study due to the small number of patients with candidemia, the predominance of *C. albicans*, the exclusion of patients with repeated ICU stay and the lower rate of empirical antifungal use.

There are some limitations of this study including a relatively smaller sample size and number of the candidemia cases due to the medical PICU patient population. In addition, 30-days mortality could not be established due to the patients being discharged from hospital shortly after ICU discharge, precluding us from drawing conclusion about mortality rate in patients who had colonization but not candidemia. Another limitation is the exclusion of newborns due to the different localization of the newborn unit in our hospital.

In conclusion, pediatric intensive care units are at risk for fungal infection. All strategies for early diagnosis and treatment are important in order to reduce morbidity and mortality. This study showed that epidemiological factors such as presence of urinary catheterization, length of stay and vancomycin use in PICU were related to increase of the *Candida* colonization index, which helps to identify high-risk patients for Candida infections, predominately candidemia. The specificity and the negative predictive value of 100% indicate that CI is a useful score to rule out the presence of invasive fungal disease. On the other hand, the low rate of sensitivity (33.3%) and positive predictive value (6.7%) make this score sometimes

unreliable in forecasting invasive candidiasis in children. More detailed and larger studies should be made to understand the complicated journey of *Candida* spp. from colonization to infection in pediatric patients.

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