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Occurrence of Candiduria in Paediatric Patients and its Antifungal Susceptibility in a Tertiary Care Centre

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Abstract

Children with urinary tract infection present with vague clinical features and candiduria in such patients signifies pyelonephritis/cystitis, disseminated candidiasis, contamination or colonisation. This study was aimed to determine the prevalence of candiduria in paediatric patients, their speciation, associated risk factors and antifungal susceptibility of these isolates which will help the clinicians in the better management of candiduria. In our study, the isolation rate for candiduria was 24.3%, more common in males (63%) compared to females (37%) and infants were most commonly involved. Colony count of $\geq 10^5$ cfu/ml seen in 53% of the isolates and pus cells were seen in 84% cases. Among candiduria cases, 87% received broad spectrum antibiotics for more than 7 days, while 57% were catheterized, and 19% of the patients were on fluconazole therapy. In the present study, non-albicans candida species emerged as the predominant pathogen and was found in 57% cases while *Candida albicans* was found in 43% cases of candiduria. Antifungal susceptibility testing revealed that all the isolates were sensitive to voriconazole and ketoconazole while 95% of the isolates were sensitive to fluconazole and 92% were sensitive to itraconazole. Resistance to fluconazole was found in 5% of isolates while 8% isolates were resistant to itraconazole. Identification of candida species along with antifungal susceptibility is important in patients with UTI and will help the clinician in selecting the appropriate antifungal agent for better management of such cases.

Keywords: Candiduria; Risk factors; Antifungal susceptibility; Non-albicans candida

Introduction

Fungal UTI (urinary tract infection) is one of the important factor in mortality and morbidity in hospitalised patients especially in paediatric population. Spectrum of disease varies from asymptomatic candiduria to clinical sepsis [1,2]. Also children present with vague clinical features like recurrent fever, diarrhoea, vomiting, abdominal pain and poor weight gain. It signifies pyelonephritis/cystitis, disseminated candidiasis or merely contamination or colonisation. However, the prevalence of true infection has increased significantly over the past few years due to the presence of various predisposing factors especially in hospitalized patients [3-5]. Risk factors for candida infections include prolonged hospitalisation, broad spectrum antibiotic therapy, use of catheter, total parenteral nutrition, renal and urinary tract malformations and prematurity [4,5]. Non-albicans Candida species appear better adapted to the urinary tract environment with many studies reporting that >50% of urinary Candida isolates belong to non-albicans species. *C. tropicalis, C. glabrata, C. parapsilosis, C. lusitaniae, C. guilliermondii and C. krusei* are common non-albicans species that cause candiduria [6]. Many non-albicans Candida spp. are inherently resistant to treatment with fluconazole and hence it is important to speciate candida and to perform antifungal susceptibility for management of paediatric UTI. Hence antifungal susceptibility is necessary. Data regarding significant candiduria amongst paediatric population is limited as most of it is reported as colonisation leading to infections going untreated and causing ascending infections and candidemia. This study was aimed to determine the prevalence of candiduria in paediatric patients (<14 years) and to assess significant candiduria and association of risk factors as these patient are more prone for disseminated candidiasis. This study also extends to determine various candida species causing UTI and its antifungal susceptibility which will help the clinicians in the better management of candiduria.

Materials and Methods

This study was conducted in the department of Microbiology of a tertiary care hospital, New Delhi from April 2014 to March 2015. Urine samples collected from paediatric and neonatal ICU and paediatric wards from suspected UTI patients who were symptomatic and were not on any antifungal treatment were received in the microbiology laboratory and were included in the study (Inclusion criteria). Paediatric patients taking antifungal agents were not included in the study (Exclusion criteria). All urine samples received from one patient were considered as a single sample. Wet mount preparations were examined for visualization of pus cells, yeast cells and culture was performed on SDA (Sabouraud Dextrose agar) slants with and without antibiotics. Slants were incubated at 37°C and 25°C and were examined after 48 hours of incubation. Semi-quantitative culture was done on blood agar plate using standard loop which holds 10 µl of urine. All yeast colonies were identified based on colony morphology, germ tube test, which was performed by putting 0.5 ml of sheep or human serum into a small tube followed by emulsification of yeast colony into it. The tube was then incubated at 37°C for 2 hours. Germ tube formation which was seen as a short hyphal (filamentous) extension arising laterally from a yeast cell, with no constriction at the point of origin was observed under high power. Other tests performed were colour appearance on CHROM agar Candida, morphology on corn meal agar, biochemical properties in sugar assimilation test and were confirmed

by automated system Microscan Walkaway 40plus system [7,8]. Three consecutive urine samples positive for yeast cells and culturing the same candida species was considered as causing UTI and the risk factors like broad spectrum antibiotics, catheterization, immunosuppression, steroid use etc. were assessed in such patients. Antifungal susceptibility testing was done by disc diffusion method as per CLSI guidelines and antifungals tested were fluconazole (25 µg), ketoconazole (10 µg), voriconazole (1 µg) and itraconazole (10 µg) (HiMedia laboratories Pvt. Ltd, Mumbai). Disc diffusion results were further confirmed by Minimum Inhibitory Concentration (MIC) using E- test strips procured from HiMedia laboratories Pvt. Ltd, Mumbai. All freshly prepared medias were tested using quality control strains ATCC 90028 (*Candida albicans*), ATCC 13803 (*C. tropicalis*), and ATCC 6258 (*C. krusei*). All the data were entered in the Microsoft excel sheet and processed for statistical analysis to calculate various percentage.

Results

In our study, the isolation rate for candiduria was 24.3% i.e., 100 candida spp. were isolated out of 412 patients included. Candiduria was more commonly seen in males (63%) compared to females (37%) and it was most common in infants (44%) followed by 6-10 yrs (21%) and 11-14 years (18%) (Table 1). In the present study, colony count of $>10^5$cfu/ml were found in 53% of the isolates followed by 10^4cfu/ml in 23% and 10^3cfu/ml in 19% isolates, however, pus cells were seen in the microscopic examination of 84% cases (Table 2). Sixty seven percent of the candida isolates were from ICUs (Intensive care unit) while 33% isolates were from children admitted in wards (Table 3). Among candiduria cases, 87% received broad spectrum antibiotics for more than 7 days, while 57% were catheterized, and 19% of the patients were on fluconazole therapy. In ICUs out of 67 isolates, 94% received prolonged antibiotic, 58.2% were catheterized and 20.9% were on fluconazole therapy (Table 4).

Age group	No. of isolates	Males	Females
<1 year	44 (44%)	31	13
1- 5 yrs	17 (17%)	10	7
6-10 yrs	21 (21%)	11	10
11-14 yrs	18 (18%)	11	7
Total	100	63 (63%)	37 (37%)

Table 1: Age-wise and sex-wise distribution of various candida isolates in paediatric population.

Colony Counts	No. of isolates	Presence of pus cells	Absence of pus cells
$>10^5$ cfu/ml	53 (53%)	45	8
10^4 cfu/ml	23 (23%)	20	3
10^3 cfu/ml	19 (19%)	15	4
$<10^3$ cfu/ml	5 (5%)	4	1
Total	100	84 (84%)	16 (16%)

Table 2: Colony counts in various candida isolates and their correlation with pus cells.

Pediatric Units	Total positive samples	Males	Females	Candida albicans	Non-albicans Candida spp.
Pediatric ICU	52 (52%)	37	15	18	34
Neonatal ICU	15 (15%)	9	6	7	8
Pediatric ward	33 (33%)	17	16	18	15
Total	100	63 (63%)	37 (37%)	43 (43%)	57 (57%)

Table 3: Distribution of candida isolates in children from ICU and wards (n=100).

In the present study, non albicans candida species emerged as the predominant pathogen and was found in 57% cases while Candida albicans was found in 43% cases of candiduria (Table 3). Among non-albicans candida, most common species were *C. tropicalis* (45%) followed by *C. parapsilosis* (7%) and *C. krusei* (5%) (Table 5). Antifungal susceptibility testing revealed that all the isolates were sensitive to voriconazole and ketoconazole while 95% of the isolates were sensitive to fluconazole and 92% were sensitive to itraconazole as shown in Table 6. All C. tropicalis isolates were found sensitive to antifungals tested. 5 (11.6%) *C. albicans* isolates were found resistant to itraconazole while all *C. albicans* were found sensitive to fluconazole, ketoconazole and voriconazole. All *C. parapsilosis* were sensitive to fluconazole, ketoconazole and voriconazole while 2 of the *C. parapsilosis* isolates were resistant to itraconazole. All *C. krusei* isolates were found resistant to fluconazole, 1 isolate was resistant to itraconazole while none were resistant to ketoconazole and voriconazole (Table 6).

Risk factors	ICU (n=67)	Ward (n=33)	Candiduria (n=100)
Broad spectrum antibiotics (>7 days)	63 (94%)	24 (72.7%)	87 (87%)
Catheterization	39 (58.2%)	18 (54.5%)	57 (57%)

Fluconazole therapy	14 (20.9%)	5 (15%)	19 (19%)
Steroid therapy	6 (8.9%)	1 (3%)	7 (7%)

Table 4: Assessment of risk factors in children with candiduria.

Etiological agents	Males (%)	Females (%)	No. of isolates	Percentage
C. albicans	27 (42.8%)	16 (43.2%)	43	43%
C. tropicalis	29 (46%)	16 (43.2%)	45	45%
C. parapsilosis	4 (6.3%)	3 (8.1%)	7	7%
C. krusei	3 (4.8%)	2 (5.4%)	5	5%
Total	63 (63%)	37 (37%)	100	-

Table 5: Distribution of various candida species in urine samples.

Candida spp.	Fluconazole	Voriconazole	Itraconazole	Ketoconazole
C. tropicalis (45)	45 (100%)	45 (100%)	45 (100%)	45 (100%)
C. albicans (43)	43 (100%)	43 (100%)	38 (88.4%)	43 (100%)
C. parapsilosis (7)	7 (100%)	7 (100%)	5 (71.4%)	7 (100%)
C. krusei (5)	0 (0%)	5 (100%)	4 (80%)	5 (100%)
Total	95 (95%)	100 (100%)	92 (92%)	100 (100%)

Table 6: Antifungal sensitivity pattern of candida isolates.

Discussion

Candida infections are an emerging problem in paediatric population especially in hospitalized patients. Candiduria is one of the important factors for mortality and morbidity in hospitals and it accounts for 5.5% of UTIs in children less than 12 yrs. In our study, isolation rate of *candida* species was found to be 24.3% which is in accordance with other study from Brazil (22%) [9]. In the present study, males (63%) were more commonly affected than females (37%) and candiduria was most common in infants (44%). This result is comparable with other study conducted by Seifi Z et al. [10] where 71.4% of candida was isolated in males and 28.6% in females [10].

Many risk factors have been suggested to candiduria, such as broad spectrum antibiotics therapy, corticosteroids agents, immunosuppressive drugs, use of indwelling catheters for urinary drainage, hematologic malignancies, urinary tract abnormalities and prematurity [4]. Long duration in ICU and prolonged hospital stay also increase the prevalence of candiduria in admitted patients and it increases further mortality and morbidity in such patients. In our study, 67% of the *candida* isolates were from ICU while 33% isolates were from children admitted in wards. The assessment of risk factors suggested that among candiduria cases, 87% received broad spectrum antibiotics for more than 7 days, while 57% were catheterized, and 19% of the patients were on fluconazole therapy. Candiduria in ICUs were more associated with risk factors compared to ward patients i.e., 94% of the cases received prolonged antibiotic, 58.2% were catheterized and 20.9% were on fluconazole therapy. Underlying risk factors were also seen in other studies [11,12]. as candida can easily colonize and form biofilm on the catheter surface, Prolonged usage of antibiotics increase the risk of colonization of *Candida spp*. by suppressing endogenous flora, and negatively affecting phagocytosis and humoral immunity leading to candiduria and it was seen as the most common risk factor for development of candiduria in our study [13,14]. There is a definite risk of invasive candidiasis following candiduria in the presence of associated risk factors, and hence aggressive approach is warranted by the clinicians.

Candiduria may be a result of contamination, colonization or indicative of invasive UTI. Quantitative cultures with colony counts of >100,000 cfu/ml of urine are associated with infection in patients without indwelling urinary catheters. However, renal candidiasis has been reported even with low colony counts of 1000 cfu/ml of urine [15]. Isolation of candida on repeated samples and presence of pus cells are also important for the diagnosis of invasive candiduria and rules out contamination or colonisation. In this study, colony count of $\geq 10^5$ cfu/ml were found in 53% of the isolates and 10^4 cfu/ml in 23% while pus cells were present in 84% of the cases. In our study counts $\leq 10^3$ were also considered significant and were processed if same candida species was isolated in three consecutive samples. Colonisation is an important risk factor for development of candidaemia with a high mortality rate of 46-80% compared with bacteraemia (38%) [16]. Also candiduria should never be ignored in septic patients, as it may be the first sign of a systemic *Candida* infection [17]. Hence, in high-risk patients, candiduria should be carefully evaluated for disseminated infection.

C. albicans was considered to be the most common pathogen in paediatric patients with nosocomial candiduria [13-19]. Our study suggests the shifting trend towards non albicans candida species (57%) compared to *Candida albicans* (43%). Amongst non-albicans candida, most common species were *C. tropicalis* (45%) followed by *C. parapsilosis* (7%) and *C. krusei* (5%). This change in etiology toward non-albicans *Candida spp*. has been seen by other authors also [9-21]. This finding is worrisome as non-albicans *Candida spp*. are more difficult to treat as few strains are intrinsically resistant to Amphotericin B (*C. lusitaniae*) and *C. tropicalis*, *C. krusei, C. glabrata* and *C. parapsilosis* are less susceptible to azoles particularly fluconazole compared to *C. albicans* [22]. Hence, identification of species along with antifungal susceptibility testing should always be performed for appropriate management of such patients. Antifungals play an important role in the management of such patients, especially infection with non-albicans *candida* species. The emergence of drug resistance among fungi has made antifungal sensitivity testing more important for management of such patients. Our study revealed that all the isolates were sensitive to voriconazole and ketoconazole while 95% of the isolates were sensitive to fluconazole and 92% were sensitive to itraconazole. All candida species were found sensitive to fluconazole except *C. krusei* (which is considered as intrinsically resistant to fluconazole). Itraconazole was found sensitive in all *C. tropicalis* isolates and resistance was seen in *C. albicans, C. parapsilosis and C. krusei*. Resistance development was also seen in other studies but fluconazole was found more resistant which is in contrast to our study. Fluconazole is considered as the first choice in the treatment of these cases because of a high concentration of active drug in the urine, cost effectiveness, safety, and better tolerability and is less likely to become resistant during treatment [23].

Conclusion

In conclusion, Candiduria is an increasingly difficult problem for clinicians to recognize and manage in paediatric population due to the presence of atypical symptoms of UTI or patients being asymptomatic which could have been a limitation in our study. Candiduria may be the first symptom of disseminated candidiasis with high morbidity and mortality especially in the presence of risk factors like immunosuppression, catheterization, fluconazole therapy and prolonged antibiotics. Identification of candida species along with antifungal susceptibility is important in patients with UTI and will help the clinician in selecting the appropriate antifungal agent for better management of such cases.

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