

Hospital-Associated Funguria: Analysis of Risk Factors, Clinical Presentation and Outcome

Mauricio Carvalho, César Maistro Guimarães,
José Ronaldo Mayer Júnior, Gisele P. Fernandes
Bordignon and Flávio Queiroz-Telles

Department of Internal Medicine, Section of Infectious
Diseases and Laboratory of Mycology - Universidade
Federal do Paraná, Brazil

Fungal urinary tract infections are an increasing problem in hospitalized patients. Funguria may be a result of contamination of the urine specimen, colonization of the urinary tract, or may be indicative of true invasive infection. In this study, we report the risk factors, clinical features, treatments and outcome in a group of 68 hospitalized patients (adults and children) with fungal isolates recovered from 103 urinary samples. Underlying medical conditions were present in most patients. In the pediatric group, urinary tract abnormalities (86%) and prematurity (19%) accounted for the majority of the cases. Diabetes mellitus (28%), nephrolithiasis, and benign prostatic hyperplasia were the most common diseases in adults. Indwelling urethral catheters were noted in 38% of the pediatric patients and in 43% of adults during hospitalization. *Candida albicans* strains were responsible for 97% and 75% of positive cultures in children and adults, respectively. Symptoms such as fever, dysuria, frequency and flank pain were generally absent in both groups. Fluconazole was the most frequent antifungal utilized (61%) in children and ketoconazole in the adult group (42%). Removing the urinary catheter was attempted in 6 pediatric patients (29%) and in only 8 adults (17%). One patient (4%) in the pediatric group died compared to 10 in the adult group (21%, $p=0.04$). Successful diagnosis and treatment of funguria depends on a clear understanding of the risk factors and awareness of fungal epidemiology.

Key Words: Funguria, candiduria, fungal infections.

The incidence of fungal infections of the genitourinary system is increasing in all areas of medical and surgical practice. The use of broad spectrum antibiotics, immunosuppressive agents, indwelling catheters for urinary drainage, and hematologic malignancies have contributed to this change [1]. In a typical general hospital, one might expect 1% to 5% of all urinary isolates to contain fungi [2].

There are specific criteria for evaluating urinary tract infections (UTI) caused by bacteria. There are also specific guidelines for the prevention of catheter-associated bacteriuria. No such criteria or recommendations are available for fungal UTI [3,4]. Funguria may signify contamination of the urine specimen, colonization of the lower urinary tract, or may be indicative of true invasive infection of the upper and/or lower urinary tract [5]. Probably for this reason, a physician's response to the finding of yeast in the urine may vary from not initiating therapy to the parenteral administration of amphotericin B [6].

In this study, we report the epidemiology in regard to risk factors, clinical features, treatments and outcome in a group of hospitalized patients with fungal isolates recovered from urinary samples.

Received on 6 September 2001; revised 21 December 2001.
Address for correspondence: Dr. Mauricio Carvalho. Rua
Chichorro Júnior, 144 – ap. 142, Curitiba – Paraná – 80035040.
Phone – (041) 2525073. Fax – (041) 2627658.
E-mail: carvalho@mais.sul.com.br

The Brazilian Journal of Infectious Diseases 2001;5(6):313-318.
© 2001 by The Brazilian Journal of Infectious Diseases and
Contexto Publishing. All rights reserved.
1413-8670

Materials and Methods

The hospital of the Paraná Federal University is a 630-bed metropolitan teaching hospital that serves a large community and provides primary and tertiary medical care to a wide variety of outpatients and inpatients. In this work, hospitalized patients with at least one urine culture positive for fungus were identified. The study period extended from January 1, 1988, through December 31, 1999. Medical records were reviewed and the following information was abstracted from each chart: age; sex; hospital service and discharge diagnoses; antibiotic therapy; major and minor surgical procedures; immunosuppressive therapy; presence or absence of any catheter; cultural data for yeasts (all sites) to identify colony counts; results of cultures from other body sites; antifungal therapy; clinical course, and outcome.

For analysis purposes, patients were divided into two groups according to age: <14 years old (pediatric patients – group I) and >14 years old (adult patients – group II).

The data are shown as mean values \pm standard error of mean. Student's *t* test was used to compare the two groups with respect to mortality and length of hospitalization. All data were analyzed with Minitab 11.2 statistical software.

Results

During the study period, 103 urine cultures positive for fungi were identified in 68 patients. Twenty-one patients had 38 urine cultures positive in group I (1.8 cultures per patient). In this group, the patients were predominantly male (81%), with a mean age of 2.35 ± 0.89 years old. In group II, there were 47 patients with 65 positive urine cultures (1.4 cultures per patient). Twenty-five were male (53%) and the mean age was 50.74 ± 3.13 years (Table 1).

In both groups, the majority of patients came from intensive care units and from nephro-urological wards (Table 1). Underlying medical conditions were present in most patients (Table 2). In the pediatric group, urinary

tract abnormalities and prematurity accounted for the majority of the cases. Diabetes mellitus, nephrolithiasis, and benign prostatic hyperplasia were the most common diseases in group II. Also, in this last group, 16 patients (34%) had been treated with corticosteroids or other immunosuppressive agents, or had some kind of immunosuppression. Sixty-six per cent of the pediatric patients and 43% of adults had recently received broad-spectrum antibiotics, most often for a bacterial UTI (Table 2).

Indwelling urethral catheters were noted in 8 (38%) patients from group I and in 20 (43%) patients from group II during their hospitalization. Suprapubic catheters or nephrostomy were rarely used.

Candida albicans strains were responsible for 97% of the positive cultures in group I and 75% in group II (Table 3). Other species were rarely isolated and included *Cryptococcus neoformans* (5 cases), *Trichosporon beigeli* (2), and *Candida tropicalis* (1 case). Of all isolates from group II, 14% were identified only as non-*albicans* species of *Candida*. Four patients in each group (4/21, 19% in group I and 4/47, 8.5% in group II) had blood cultures positive for *Candida*. In 3 patients from group I, candiduria was the first evidence of disseminated candidiasis. Urinalysis detected the presence of fungi in 53% of the cases in group I and in 32.5% of the patients in group II (10/19 and 12/37, respectively). Hematuria was present in 68% of the cases in both groups, and pyuria in 7 cases (37%) in the pediatric group and in 16 cases (43%) in the adult group. Symptoms such as fever, dysuria, frequency, and flank pain were generally absent. Only 4 patients (19%) in Group I and 6 patients (13%) in Group II had these findings recorded.

Underlying conditions were present in all 5 adults with *Cryptococcus neoformans*. Three were HIV positive, one had a kidney transplant and another patient presented with septic shock caused by Gram negative bacteria.

In response to culture-results, clinicians initiated antifungal therapy 13 times in Group I and 21 times in Group II. Treatment was often based on a single culture without documenting the site of infection inside the urinary tract and without a follow-up urine culture performed.

Table 1. Characteristics of the patients

Characteristic	Group I (Pediatric patients) n=21	Group II (Adult Patients) n=47
Age - years (mean)	2.35 ± 0.89	50.74 ± 3.13
Range	0 – 13 years old	16 – 86 years old
Sex – M / F	17 / 4	25 / 22
Year of hospitalization		
1988 to 1993	4 (19%)	34 (72%)
1994 to 1999	17 (81%)	13 (28%)
Hospital unit		
Intensive care unit	12	19
Nephrology department	8	6
Urology department	1	5
Other	0	17

Table 2. Underlying diseases or conditions

Underlying disease or condition	Group (Pediatric patients) n=21	Group II (Adult patients) n=47
Diabetes Mellitus	2 (9.5%)	13 (28%)
Prematurity	4 (19%)	-
Urinary tract disease	18 (86%)	22 (47%)
Myelomeningocele/neurogenic Bladder	5	1
Prostatic hyperplasia	0	9
Stones	2	8
Recurrent urinary infection	6	4
Posterior urethral valve	5	0
Catheterization	8 (38%)	20 (43%)
Recent antibiotics	14 (66%)	20 (43%)
Immunosuppression / transplant	1 (5%)	16 (34%)
Other	5 (24%)	5 (11%)

Table 3. Fungal species isolated from urine

Fungal species	Group I (Pediatric patients) Number of positive cultures = 38	Group II (Adult patients) Number of positive cultures = 65
<i>Candida albicans</i>	37 (97%)	49 (75%)
<i>Candida tropicalis</i>	1 (3%)	0
<i>Candida</i> sp.	0	9 (14%)
<i>Cryptococcus neoformans</i>	0	5 (8%)
<i>Trichosporon beigelli</i>	0	2 (3%)

Fluconazole was the most frequent antifungal used (8 of 13, 61%) in Group I, and ketoconazole in Group II (8 of 19, 42%), followed by amphotericin B. Removing the urinary catheter was attempted in 6 pediatric patients (29%) and in 8 adults (17%).

One patient (4%) from the pediatric group died compared to 10 from the adult group (21%, $p=0.04$). In Group II, only 2 patients were judged to have died of complications related to funguria. The length of hospitalization was 41 ± 10 days in group I and 28 ± 4 days in adults patients ($p=NS$).

Discussion

Fungal UTI has become an important problem over the past decade [7]. Despite its prevalence, the significance of funguria remains uncertain. The disorder lacks consistent diagnostic criteria, such as the presence of pyuria or a colony count above which predicts the presence, location, or severity of infection [8]. Pediatric patients have been studied even less frequently, and important differences were noted when compared with adults [9].

The pathogenesis of candidal UTI has been relatively well characterized and many risk factors have been identified [10-12]. In our study, most of the pediatric patients had underlying diseases, mainly urinary tract abnormalities and prematurity. Premature infants with extremely low body weight are more susceptible to fungal infection but do not seem to have urinary tract abnormalities [13].

In adults, we found that diabetes mellitus, nephrolithiasis, prostatic hyperplasia, and use of immunosuppressive agents were the most frequent comorbid conditions. Kauffman, et al., also described several of these risk factors in their prospective multicenter surveillance study [14]. They emphasized that a diagnosis of diabetes mellitus was associated with nonclearance of funguria when no antifungal therapy was given.

Antibiotic use prior to detection of fungus in urine was very common in our study, occurring in 66% of pediatric patients and in 43% of adults. The change in the normal flora of the perineum allowing overgrowth of yeasts is the presumed cause [15].

It has long been recognized that the presence of an indwelling catheter favors the development of funguria

[16,17]. The present study confirmed this fact. In the pediatric group 38% of the patients, and 43% of the adult patients were catheterized during hospitalization. Many of our patients from both groups came from intensive care units or had urinary abnormalities that increase the need for bladder drainage devices.

Candida albicans was the most common fungus isolated in our study, responsible for 97% of positive cultures in group I and 75% in group II. This finding is confirmed by several studies, but in recent years a trend towards recovery of different specimens is rising [14, 18]. Although we did not find an increase in a given *Candida* species, 14% of urine cultures from adult patients were identified only as *Candida* sp. Candidemia is rarely the consequence of candiduria [18]. In our experience, 14% of pediatric patients presented with candiduria as the first evidence of disseminated candidiasis (pulmonary and central nervous system). All patients had some structural abnormality in the upper urinary tract.

Less than one third of episodes of candiduria were treated with antifungals. Most frequently, clinicians judged that funguria was not important or that culture reflected colonization or was contaminated. Even when the urine culture was repeated and revealed positive, the most frequent therapeutic decision was not to treat. Several authors reported the same experience [14,19]. Follow up cultures were not sufficiently frequent to analyze the evolution of funguria with or without treatment in this study.

The mortality rate among pediatric patients was very low (4%) compared to adults (21%). Even in this group, only 2 patients were presumed to have died from complications of fungal infection. The high mortality rate of adult patients probably reflects multiple underlying diseases and not the candiduria per se, as noted by Jacobs, et al. [20].

In conclusion, our study showed that patients with fungal infections in urine have multiple risk factors related to urinary tract or systemic diseases. Funguria is also associated with the use of antibiotics and corticosteroids. *Candida albicans* was the most common yeast isolated and candiduria may precede candidemia in some occasions. Death directly related

to urinary fungal infections is uncommon. Efforts directed at clinicians' awareness of funguria, with the intention to confirm the diagnosis and stratify treatment according to risk factors, appear to be both necessary and worthy of the time and effort required [19].

References

1. Frangos D.N., Nyberg Jr. L.M. Genitourinary fungal infections. *South Med J* **1986**;79:455-9.
2. Simsek U., Akinci H., Oktay B., et al. Treatment of catheter-associated Candiduria with fluconazole irrigation. *Br J Urol* **1995**;75:75-7.
3. Hamory B.H., Wenzel R.P. Hospital-associated candiduria: predisposing factors and review of the literature. *J Urol* **1978**;120:444-8.
4. Cox G.M., Perfect J.R. Fungal infections of the kidney and those associated with renal failure, dialysis and renal transplantation. In: Kibbler C.C., Mackenzie D.W.R., Odds F.C. eds. *Principles and Practice of Clinical Micology*. New York: John Wiley & Sons Ltd, **1996**.
5. Vazquez J.A., Sobel J.D. Fungal infections in diabetes. *Infect Dis Clin North Am* **1995**;9:97-116.
6. Fisher J.F., Newman C.L., Sobel J.D. Yeast in the urine: solutions for a budding problem. *Clin Infect Dis* **1995**;20:183-9.
7. Beck-Sague C.M., Jarvis W.R. National Nosocomial Infections Surveillance System. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. *J Infect Dis* **1993**;167:1247-51.
8. Sobel J.D. Fungal diseases in genitourinary medicine. In: Kibbler C.C., Mackenzie D.W.R., Odds F.C. eds. *Principles and Practice of Clinical Micology*. New York: John Wiley & Sons Ltd, **1996**.
9. Trnka P., Kralik J., Pevalova L., et al. Candiduria in critically ill children: risk factors and predictors of mortality. *Infect Dis Clin Pract* **1998**;7:234-9.
10. Oravcova E., Lacka J., Drgona L., et al. Funguria in cancer patients: analysis of risk factors, clinical presentation and outcome in 50 patients. *Infection* **1996**;24:319-23.
11. Krcmery S., Dubrava M., Krcmery Jr. V. Fungal urinary tract infections in patients at risk. *Int J Antimicrob Agents* **1999**;11:289-91.
12. Talluri G., Marella V.K., Shirazian D., Wise G.J. Immune response in patients with persistent candiduria and occult candidemia. *J Urol* **1999**;162:1361-4.
13. Chun C.S., Turner R.B. The outcome of candiduria in pediatric patients. *Diagn Microbiol Infect Dis* **1991**;14:119-23.

14. Kauffman C.A., Vazquez, J.A., Sobel J.D., et al. Prospective multicenter surveillance study of funguria in hospitalized patients. *Clin Infect Dis* **2000**;30:14-8.
15. Fisher J.F., Chew W.H., Shadomy S., et al. Urinary tract infections due to *Candida albicans*. *Rev Infect Dis* **1982**;4:1107-18.
16. Schönebeck J., Anséhn S. The occurrence of yeast-like fungi in the urine under normal conditions and in various types of urinary tract pathology. *Scand J Urol Nephrol* **1972**;6:123-8.
17. Schönebeck J. Asymptomatic candiduria. Prognosis, complications and some other clinical considerations. *Scand J Urol Nephrol* **1972**;6:136-46.
18. Sobel J.D., Kauffman C.A., McKinsey D., et al. Candiduria: A randomized, double-blind study of treatment with fluconazole and placebo. *Clin Infect Dis* **2000**;30:19-24.
19. Ayeni O., Riederer K.M., Wilson F.M., Khatib R. Clinicians' reactions to positive urine culture for *Candida* organisms. *Mycoses* **1999**;42:285-9.
20. Jacobs L.G., Skidmore E.A., Freeman K., et al. Oral fluconazole compared with bladder irrigation with amphotericin B for treatment of fungal urinary tract infections in elderly patients. *Clin Infect Dis* **1996**;22:30-5.