Risk factors for nosocomial candiduria

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ABSTRACT

Objective: To investigate the risk factors and the *Candida* species that cause candiduria in hospitalized patients via a case-control study.

Methods: We evaluated the results of the urine analysis of the specimens sent to the laboratories of Central Microbiology and the Department of Clinical Bacteriology and Infectious Diseases of Selcuk University Medical School, Konya, Turkey between January and December 2004. The urinary specimens, sent from hospitalized patients, obtained within 72 hours were evaluated. A total of 51 patients above 17 years of age, without any bacterial growth in urine specimens, with fever above 38ºC and pyuria were included in this study. A control group of 153 patients without any bacterial growth at 72 hours after hospitalization was present. The average age of the patients, the hospitalization period, and clinics resemble each other in the 2 groups.

Results: Risk for candiduria was increased by 4 folds (p=0.001; OR=4.020) in abdominal surgery, by 1.4 folds (p=0.335; OR:1.478) in corticosteroid and immune suppressive therapies and by 12 folds (p=0.000; OR=12.408) in urinary catheterization, antibiotic use increased the risk of candiduria by 6 folds (p=0.000; OR=6.00). The risk of candiduria was higher by 2 folds in diabetes mellitus patients than in the controls (p=0.044; OR=2.002).

Conclusion: *Candida albicans* (68.62%) was the most commonly isolated agent in candiduria patients. We should decrease the use of urinary catheters and avoid excess use of antibiotics as much as possible in hospitalized patients.

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Nosocomial infections are important health issues for both developed and developing countries. Among these, urinary tract infections are the most frequent one. Moreover, *Candida albicans (C. albicans)* is the most common agent that is isolated from urinary infections of fungal origin.

Candida albicans is present in the normal gastrointestinal and oropharyngeal flora.[1] Changes in the defense mechanisms of the host result in a favorable environment for the reproduction of C. albicans. Unless the impaired condition of the host's immunity is corrected, recovery is quite difficult to occur even when the necessary treatment modalities are administered.[2]

In this survey, we aimed to determine the risk factors (malignancy, pregnancy, urinary system abnormalities, which cause obstruction, diabetes mellitus, urinary system interventions, use of antibiotics, immune suppression or corticosteroid administration, abdominal surgery) for candiduria and isolate the candida subtypes involved, via a case-control study.

Methods. In this study, we evaluated the results of the urine analysis of the specimens sent to the laboratories of Central Microbiology and Department of Clinical Bacteriology and Infectious Diseases of

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Selcuk University Medical School, Konya, Turkey between January and December 2004. We identified 51 cases with pyuria with candidal growth more than 100,000 cfu/ml, however no bacterial growth was present and fever was above 38˚C. We then evaluated the risk factors for these medical conditions. Patients who had bacterial growth within 72 hours following hospitalization, were below 17 years of age or also had candidemia were excluded from the study. Three patients from the same clinic with similar demographic characteristics and hospitalization periods were matched with each subject with candiduria, and a case-control study was performed in order to establish the risk factors for developing candiduria.

Selection of the patient and control groups. The patients who had candiduria were interviewed, and questioned for age, gender, department of hospitalization, malignancy, pregnancy, urinary system abnormalities that caused obstruction (congenital genitourinary abnormalities, nephrolithiasis, neurogenic urinary vesicle, urogenital tuberculosis, abnormalities of the ureteropelvic junction), diabetes mellitus, interventions (urinary catheterization, stent administration, replacement of nephrostomy catheter, major urinary system surgery, extracorporeal lithotripsy), use of antibiotic treatment with corticosteroids or immunosuppressives, duration of hospitalization, and abdominal surgery.

All patients who did not show any bacterial growth in their urine specimens and were hospitalized in the clinic where there was at least one patient with candiduria were evaluated for same aspects while forming the control group. Following the constitution of the study group, some characteristics such as age, gender, duration and department of hospitalization were determined. Afterwards, 3 controls (153 controls in total) with similar characteristics (age, gender, duration and department of hospitalization, clinics) were determined for each patient recruited in the study. The average age of the patients, the hospitalization period, and clinics resemble each other in the 2 groups.

Culture and isolation. Clean catch urine specimens were obtained from patients under sterile conditions who did not have urinary catheters. In patients who did have urinary catheters, sterile urine specimens were obtained via syringes after cleaning the catheters with an antiseptic solution. Sterile urine specimens were transferred to 5% sheep blood agar and Sabouraud dextrose agar. The culture media were left for incubation for 243 hours and then evaluated microbiologically. Colonies, which smelled characteristically and were cream-like with a 0.5-1 mm thickness, were examined under light microscope either with Gram staining and ×1000 magnification or direct ×400 magnification with physiological saline. The specimens that were suspected to have *Candida* ≥100,000 cfu/ml were differentiated automatically via Mini API (Bio Merieux, France) tool in the microbiology laboratory.

Statistics. Data obtained from candiduria and control groups were analyzed using the SPSS for Windows (Real state corporation, UK) software. Students T and Chi-Square tests were employed for statistical analyses and for determining the differences between case and control groups in terms of the risk factors. Levels below 0.05 were accepted as statistically significant.

In order to determine the effect of each risk factor on the development of candiduria, estimated relative risk values [ODDS ratios (OR)] were calculated and expressed with 95% confidence intervals. In certain cases in which OR values were different from one, given that one is not included in the range of the confidence interval, decrease or increases in the risk were considered to be significant.[3]

Results. Risk factors for candiduria were evaluated in this study. Twenty-nine females (56.9%) and 22 males (43.1%), constituting a total of 51 patients, were evaluated. In the control group, 87 females (57.2%) and 66 males (42.8%) were included. There was no significant difference between the 2 groups in terms of the gender variant (p=1.000; t=2:0.000). Mean age of the subjects was 47.96 ± 17.06 (ranging between 18-76 years) and that of the controls was 47.59 ± 16.65 (ranging between 17-79 years). There was no significant difference between mean ages of the 2 groups (p=0.892; t=0.136).

Mean duration of hospitalization was 17.14 ± 15.50 days in the case group and 14.14 ± 7.48 days in the control group. Both groups were similar in terms of the mean duration of hospitalization (t=1.328; p=0.189). Distribution of subjects among the groups was not statistically different in terms of age and duration of hospitalization.

Twenty-three of the subjects (45.1%) were hospitalized in the Intensive Care Unit and the rest (54.9%) were hospitalized in the services. The same numbers were recorded as 67 (43.7%) and 86 (56.3%), respectively, in the control group. Distribution of the subjects in between the groups was not statistically different (t=0.02, p=0.963) in terms of the department of hospitalization. Comparison of candiduria and control groups revealed that the risk for developing candiduria was 12 times higher with administration of urinary catheter, 6 times higher in the presence of urinary pathologies, 6 times higher in use of wide

Table 1 - Comparison of the patient group with candiduria and the control group in terms of risk factors.

Risk factors	Cases	Controls	χ^2	UD	*P*	OR	CI
Malignancy	4/51	43/153	8,856	1	0,003	0,218	0,74 - 0,641
Antibiotic use	45/51	85/153	17,67	1	0,000	6,00	2,42 - 14,89
Diabetes mellitus	19/51	35/153	4,063	1	0,044	2,002	1,013 - 3,957
Urinary catheter	41/51	38/153	49,752	1	0,000	12,408	5,674 - 27,136
Urinary pathology	14/51	8/153	19,632	1	0,000	6,858	2,677 - 17,569
Abdominal surgery	13/51	12/153	11,078	1	0,001	4,020	1,697 - 9,523
Steroid use	11/51	24/153	0,931	1	0,335	1,478	0,666 - 3,280
UD - unlimitedness degree, OR - odds ratio, CI - confidence interval							

spectrum antibiotics, 4 times higher with abdominal surgery, 2 times higher in the presence of diabetes mellitus, one times higher with the administration of corticosteroids and 0.2 times higher in the presence of malignancies. The comparison of the patient group with candiduria and the control group in terms of the risk factors is presented in **Table 1**.

After the evaluation of the data of the 51 subjects, *C. albicans* was determined in 35 of the subjects (68.85%), and candidias of non *C. albicans* type were detected in 31.8%. The non-*C. albicans* species isolated in our study were *Candida glabrata (*11.76%), *Candida kefry (*9.8%), *Candida famata (*3.92%), *Candida sake* (3.92%) and *C. intermedia* (1.96%).

Discussion. *Candiduria* indicates the presence of *Candida* species in the urine.[4,5] The incidence of candiduria is estimated to be 6.5-20% among hospitalized patients.[6] Common risk factors for candiduria are antimicrobial therapy, female gender, urinary tract abnormality, diabetes, presence of Foley catheter, older age, cancer, immunosuppressive therapy and abdominal surgery.[7-20]

Development of urinary infections is more common in females due to anatomical and functional reasons.[7] Naturally, the incidence of candiduria is also higher among females. However, no significant difference was determined between the groups in terms of gender in the comparison of the case and control groups, since both groups had equal gender ratios.

Advanced age is known to be another risk factor in the development of candiduria. In their study, Sobel and colleagues[8] compared the effects of Fluconazole with those of placebo, and reported that the mean age of cases as 70.2 ± 1.2 years.[8] The same value was reported as 65 in the study of Febre and colleagues[9] 67 in the study of Ang and colleagues[6] and 75 in the study of Jacobs and colleagues.[10] Harris et al[11] reported the mean age for *Candida glabrata* and *C. albican*s infections as 66 years. Despite these studies, which suggest advanced age as a risk factor, Kobayashi et al[7] found the mean age of their study population with candiduria to be 48 ± 19.8 years. The mean age was 41.69 ± 17.06 years in our study.

Diabetes mellitus is known to be another risk factor for candiduria. The mechanism for its contribution to fungal infections is not clear. Presence of DM was found 37.2% in our cases. Oravcova and colleagues[12] found diabetes mellitus to be a risk factor in 15% of the patients with candiduria. Occhipinti et al[13] demonstrated the presence of diabetes mellitus in 12% of 50 the cases with candiduria.In their multi-center surveillance study that included 861 patients, Kauffman et al[14] found the incidence of DM to be 39%. The incidence of DM as a risk factor in candiduria was reported as 12-40% in various studies. When compared with the control group, we found that the risk of candiduria was increased by 2 folds in diabetic patients (OR=2.002, *p*=0.044).

Use of wide spectrum antibiotics is common particularly in the university hospitals.[15] This condition is determined to be the most important cause of the increase in the prevalence of candidal infections.[7,14] Various mechanisms are proposed in order to explain the relationship between the use of antibiotics and candiduria.[15] It was shown that antibiotics impaired phagocytic activity and antibody synthesis and consequently decreased the resistance of the host against candidal invasion.[14,15]

Weinberger and colleagues[15] established a strong relationship between candiduria and use of

wide spectrum antibiotics such as carbapeneme or cephtazidim in their series of 751 patients (for meropeneme r=0.79, p<0.001, for cephtazidim r=0.66, *p*<0.001). Kauffman and colleagues[14] determined the presence of antibiotic use in 90% of 861 patients. Kobayashi et al[7] reported that history of antibiotic use was present in 100% of the patients. Anti-microbial treatment was reported to be a risk factor for candiduria in 70-100% in various studies. It was found 88.2% in our cases. When compared with control group, we found that the risk of developing candiduria was increased by 6 folds in patients with a history of antibiotic use (OR=6.00; *p*=0.000).

History of urinary catheter administration or urinary system surgery is present in most of the patients with candiduria.[7,16] Orovcova et al[12] reported candiduria in 23 of 50 patients who had a history of urinary catheter administration or nephrostomy, and they concluded that these procedures were risk factors for candidal infections. The rate for catheter use was reported as 84.4% by Kobayashi et al,[7] and 54% by Occhipinti and colleagues[13] in patients with candiduria. Both values were evaluated to be significant. In their multi-center surveillance study, which included 861 patients, Kauffman and colleagues[14] reported that 83% of the patients had a history of use of any instruments for urinary discharge. Presence of urinary catheter administration was found 80.3% in our cases. It has been reported that use of instruments for urinary discharge, and catheters were risk factors for candiduria. We found that candiduria risk increased by 12 folds in the presence of urinary catheters (OR=12.408; *p*=0.000).

Use of steroids was also reported to be a risk factor for the development of candiduria.[17,18] Besides, immune suppressive agents, which were used following organ transplantations, were reported to increase the incidence of urinary system infections. Corticosteroids are generally used in combination with immune suppressive agents such as azathioprine and cyclosporine. These agents suppress normal immune mechanisms of the host against *Candida* species. It was thought that the decrease in host immunity resulted in an increase in the virulence of fungi.[17] Orovcova and colleagues[12] reported that 72% of the patients with candiduria received corticosteroid treatment, and they concluded that this treatment modality was among the risk factors of candidal infections. The use of corticosteroids was found 80.3% in our cases. We found that candiduria risk was increased by 1.4 times with the use of corticosteroids or immune suppressive agents (OR=1.478; p=0.335).

Fungal infections are observed frequently in malignant subjects.[12,19] It has been reported that besides the bacterial infections, which occur concomitantly with febrile neutropenic attacks, previously undetected *Candida* infections also manifested themselves in the form of candidemia and urinary tract infections.[1] Cancer was found in 7.8% in patients. We found that the risk of developing candiduria was 0.2 times higher in the presence of malignancies (OR=0.218; *p*=0.003).

Surgery is known to be a risk factor for urinary candidiasis, however, its mechanism is unclear. Ang and colleagues[6] showed that history of surgical intervention including the urinary system performed in the last 2 weeks was present in 73% of the patients with candiduria. Kobayashi and colleagues[7] reported that there was history of surgical intervention in 66.7% of the patients with candiduria, and the presence of surgical intervention was established to be an effective risk factor for the development of candiduria. We found history of abdominal surgery in 25.4% of patients and 4 times greater risk of candiduria (OR=0.218; p=0.001).

Candida albicans is the most common isolate in urine specimens.[5,15,20] Among all fungi isolated from the urine, 40-65% was found to be *C. albicans*.[1] Kauffman and colleagues[14] reported that *C. albicans* was present in 51.8% and *C. glabrata* was present in 15.6% of the patients with candiduria.[14] In their study performed with 751 patients, Weinberger and colleagues isolated *C. albicans* in 56.4%, *C. tropikalis* in 19%, *C. glabrate* in 15.7%, *C. parapsilosis* in 6.1%, *C. krusei* in 1.8%, *C. kefry* in 0.7% and *C. lipolytica* in 0.1% of the cases.[15] Although the prevalence of *Candida albicans* is higher, the proportion of non-*Candida* fungi involved in urinary pathologies increases over the course of time.[1] Orovcova and colleagues[12] observed *C.albicans* in 72% of the cases and non-*Candida albicans* pathogens in 28%, in their series of 50 patients.[12]

The most common pathogen is *Candida albicans* (21-72%), and *Candida glabrata* comes the second (5-33%). We determined *C. albicans* in 68.62%, *C. glabrate* in 11.76%, *C. kefry* in 9.8%, *C. famata* 3.92%, *C. sake* in 3.92% and *C. intermedia* in 1.96% of the cases. We found that the most common agent was C. albicans and this finding is consistent with those of the other studies.

Our study demonstrated that the presence of urinary catheters, urinary tract abnormality, use of wide spectrum antibiotics, abdominal surgery, diabetes mellitus, use of corticosteroids and immune suppressive agents, presence of malignant diseases are risk factors for candiduria. We should decrease the unnecessary use of urinary catheters, shorten the duration of catheterization and avoid excess use

of antibiotic as much as possible in hospitalized patients.

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