Catheter-associated candiduria: Risk factors, medical interventions, and antifungal susceptibility

Dan Padawer BSc, Nina Pastukh BSc, Orna Nitzan MD, Kozitta Labay RN, MHA, Ilana Aharon RN, MHA, Diana Brodsky MSc, Tatyana Glyatman MSc, Avi Peretz PhD

*Faculty of Medicine in the Galilee, Bar Ilan University, Safed, Israel
bClinical Microbiology Laboratory, Baruch Padeh Medical Center, Poriya, Affiliated with the Faculty of Medicine in the Galilee, Bar Ilan University, Israel

Key Words: Candiduria, Candida, Catheter-associated candiduria, Urinary tract infection, Catheter, Susceptibility

**Background:** Catheter-associated candiduria is a common clinical finding in hospitalized patients, especially in the intensive care unit. The objective of this study was to obtain demographic and clinical data regarding the prevalence of Candida spp in catheterized in-patients and the medical interventions provided to these patients in a northern Israeli hospital between 2011 and 2013.

**Methods:** Isolation and identification of microorganisms were performed on 1,408 urine culture samples 48 hours after catheter insertion. Antifungal Etest susceptibility tests were carried out on every Candida-positive urine sample. Demographic and clinical data were gathered to determine risk factors and medical interventions.

**Results:** Candiduria was detected in 146 catheterized in-patients out of the 1,408 patients included in this study. C. albicans was detected in most cases (69.1%). Fever was observed in 52 (35.61%) patients, and leukocyturia was observed in 48 cases (32.87%). Diabetes mellitus was associated with C. albicans candiduria. There were 93 patients (63.69%) who did not receive any medical intervention for their candiduria.

**Conclusion:** Candida is the second leading pathogen causing catheter-associated urinary tract infection or asymptomatic colonization, whereas previous studies showed Candida as the third leading pathogen. Clinical signs and symptoms, such as fever and laboratory tests, cannot distinguish between asymptomatic colonization and infection. Because the management of catheter-associated candiduria is still controversial, additional studies should be carried out.

Copyright © 2015 by the Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

---

The presence of microorganisms such as Candida spp in urine samples of hospitalized patients is a common clinical finding. Candida, a saprophytic yeast, colonizes the mucosal surfaces and external genitalia of both men and women, especially in premenopausal women’s urethral meatus area. In the general population, >1% of urine samples contain Candida in a measurable quantity; however, in hospitalized patients this rate is 5-10 times higher. Most hospitalized patients diagnosed with candiduria or Candida urinary tract infection (UTI) were treated at intensive care units (ICUs) or had a urethral catheter.

Candida spp account for 20% of the UTIs in the setting of ICUs. They are considered to be the second leading pathogen causing UTI in ICUs after Escherichia coli.

Most cases of candiduria are nosocomial because of the use of catheters and antibiotic therapy. Women are more likely to develop candiduria. Advanced age, ICU hospitalization, surgery, and pre-existing diabetes mellitus are other known risk factors for candiduria.

Candida has 3 categories of severity: (1) colonization or contamination—asymptomatic (most common presentation), (2) UTI—cystitis or pyelonephritis, and (3) systemic infection, mostly in immunocompromised patients.

Catheter-associated urinary tract colonization is the leading cause of secondary nosocomial infection in hospitalized patients. Candida is unavoidable in 50% of patients with urethral catheters for >5 days.

Catheter-associated UTI can be extraluminal (entrance of microorganisms through the catheter biofilm to the urine bladder), as in most cases, or intraluminal (urine stasis caused by drainage...
failure or ascending infection caused by contamination of the urine collection bag.\textsuperscript{15}

The lower urinary tracts are commonly the primary infection site.\textsuperscript{3} In rare conditions, the infection can spread toward the kidneys and damage their parenchyma and cause candidiasis. This can happen in the setting of urinary tract obstruction. Hematogenous spread of Candida to the kidneys is possible in immunocompromised patients.\textsuperscript{7-9}

The decision whether to treat catheter-associated candidiasis is controversial because candidiasis can be a sign of colonization where treatment is not required or upper or lower UTI where treatment is mandatory. Previous studies\textsuperscript{10} and current guidelines\textsuperscript{11} recommend catheter removal (or replacement) and controlling other risk factors as first-line therapy in asymptomatic candiduria. Postcatheterization asymptomatic candidiasis usually resolves without specific antifungal therapy. Current recommendations are to not administer antifungal agents unless the patient is symptomatic or at high risk for dissemination, such as postrenal transplant patients, low birth weight infants, and patients who are undergoing urinary tract instrumentation. When antifungal treatment is considered, amphotericin B, fluconazole, and voriconazole are the recommended antifungal agents.\textsuperscript{12-14}

The aim of this study is to obtain demographic and clinical data regarding the prevalence of Candida spp in catheterized in-patients and the medical interventions provided to these patients in a northern Israeli hospital between 2011 and 2013. In addition, susceptibility of Candida spp obtained from catheterized patients to common antifungal agents was tested.

\section*{Materials and Methods}

\textbf{Patient characteristics}

There were 1408 hospitalized patients with urethral catheters included in this study. All patients were hospitalized between 2011 and 2013 at our medical center, a 300-bed general hospital in northern Israel. Pediatric patients were not included in this study. Of the patients, 506 were women (36\%), and 902 were men. The mean age was 58.5 years. At least 1 urinary sample was obtained from each patient 48 hours after urinary catheter installation. All demographic and medical data were obtained from the hospital’s digital medical records.

\textbf{Culture and antifungal susceptibility tests}

Every urine sample was sent to the clinical microbiology laboratory in a sterile container. All samples were refrigerated up to 12 hours from the time they were obtained. Samples were inoculated using a 1-\textmu L calibrated loop on CHROMagar Orientation (BD Diagnostics, Sparks, MD), which is a chromogenic agar that allows the preliminary identification of uropathogens. Plates were examined after incubation of 24 and 48 hours at 37\textdegree C. Significant candiduria was defined as the growth of \textgtr 10,000 colony forming units/mL. Candida growth was initially identified by microscopic examination of suspected colonies. Later, those colonies were transformed to CHROMagar Candida agar (hy-labs, Rehovot, Israel), which allows Candida specification by colony color: C albicans (light to medium green), C krusei (mauve to rose pink), and C tropicalis (dark blue to metallic blue, with or without halos). The VITEK 2 (bioMérieux, Marcy l’Etoile, France) automated microorganism identification system was used to specify colonies that were not categorized. Candida Etest susceptibility examinations to antifungal agents fluconazole, voriconazole, and amphotericin B were carried out on RPMI 1640 Agar with MOPS and 2% Glucose (hy-labs, Rehovot, Israel). The Candida colony was fluidized in a 0.85% NaCl solution creating a 0.5 McFarland standard solution. Plates were incubated in 35\textdegree C for 48 hours until susceptibility results were noted. Candida was considered susceptible to antifungal agents according to the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing breakpoints.\textsuperscript{15,16}

\textbf{Statistical analysis}

Student t test was used to determine the difference of risk factors between C albicans and nonalbicans Candidas. P < .05 was considered significant.

\section*{Results}

Out of the 1,408 patients that were included in this study, 749 had a positive urine culture (53.20\%), 603 were positive for bacteria (40.51\%), and 146 grew Candida (19.49\%). Candida was the second most prevalent organism in urine cultures (after E coli) (Table 1). C albicans was identified in 101 (69.17\%) of all Candida positive samples. The mean age of patients with Candida positive urine culture was 63.7 years. Of the patients, 94 (67.1\%) were women. Most of the patients were hospitalized in the ICU (n = 67, 46\%) and in the internal medicine departments (n = 59, 40\%). The other patients were hospitalized in the surgery-urology department (n = 16, 11\%) and obstetrics and gynecology department (n = 4, 3\%). Fifty-two patients (35.61\%) had fever and 48 patients (32.87\%) had leukocytes in their urine sample. Candida spp were visible in the urine sediment of 41 patients (28.08\%). Seventeen patients (11.64\%) had fungal-bacterial coinfection and colonization. Sixty-eight (46.57\%) of the patients received antibiotics. Nineteen patients (13.01\%) had pre-existing diabetes mellitus, 13 patients (8.9\%) were immunosuppressed, and 9 patients (6.16\%) had cancer. No candidemia cases were reported in the patients included in this study. Table 2 summarizes the clinical features of all catheter-associated candidiasis.

\textbf{Table 1}

Organisms that were specified in all positive urine cultures

\begin{tabular}{|l|c|}
\hline
Organism & n (%) \\
\hline
Escherichia coli & 294 (39.25) \\
Candida & 146 (19.49) \\
C albicans & 101 (69.17) \\
C parapsilosis & 14 (9.58) \\
C krusei & 11 (7.53) \\
C tropicalis & 9 (6.16) \\
C glabrata & 7 (4.79) \\
Other Candida & 11 (7.53) \\
Pseudomonas & 114 (15.22) \\
Enterococcus & 76 (10.15) \\
Klebsiella & 68 (9.08) \\
Proteus & 30 (4.01) \\
Other & 21 (2.94) \\
\hline
\end{tabular}

\textbf{Table 2}

Clinical features of catheter-associated candidiasis

\begin{tabular}{|l|c|}
\hline
Clinical feature & n (%) \\
\hline
Fever & 52 (35.61) \\
Leukocyturia & 48 (32.87) \\
Bacterial coinfection and colonization & 17 (11.64) \\
Candida in urine sediment & 41 (28.08) \\
Antibiotic use & 68 (46.57) \\
Immunosuppression & 13 (8.98) \\
Diabetes mellitus & 19 (13.01) \\
Malignancy & 9 (6.16) \\
Candidemia & 0 (0) \\
\hline
\end{tabular}
Most patients (n = 93, 63.69%) did not receive any medical or diagnostic intervention after the diagnosis of candiduria. Catheter removal was the most common intervention (n = 43, 29.45%) followed by repeated urine culture (n = 26, 17.8%) and antifungal medication administration (n = 5, 3.42%) (Table 3).

The mean minimal inhibitory concentration (MIC) of amphotericin B, fluconazole, and voriconazole of all Candida spp were 0.269, 0.241, and 0.109 μg/mL, respectively (Fig 1, Table 4). The susceptibility of C albicans to antifungal agents revealed the following MIC: amphotericin B (0.205 μg/mL), fluconazole (0.25 μg/mL), and voriconazole (0.111 μg/mL). The susceptibility of C krusei to antifungal agents revealed the following MIC: amphotericin B (0.295 μg/mL), fluconazole (0.299 μg/mL), and voriconazole (0.114 μg/mL). The susceptibility of C glabrata to antifungal agents revealed the following MIC: amphotericin B (0.895 μg/mL), fluconazole (0.211 μg/mL), and voriconazole (0.118 μg/mL). The susceptibility of C parapsilosis to antifungal agents revealed the following MIC: amphotericin B (0.205 μg/mL), fluconazole (0.25 μg/mL), and voriconazole (0.111 μg/mL). The susceptibility of C tropicalis to antifungal agents revealed the following MIC: amphotericin B (0.167 μg/mL), fluconazole (0.1 μg/mL), and voriconazole (0.099 μg/mL). The susceptibility of other Candida spp to antifungal agents revealed the following MIC: amphotericin B (0.294 μg/mL), fluconazole (0.22 μg/mL), and voriconazole (0.074 μg/mL).

Three Candida isolates (2.05%) are considered resistant to amphotericin B according to CLSI and EUCAST clinical breakpoints. Two of them are C glabrata isolates (28.51%), and the other is a C parapsilosis isolate (7.14%). No resistant isolates to fluconazole or voriconazole were found in this study (except C krusei isolates, which are considered to be intrinsically resistant to fluconazole and C glabrata isolates where no sufficient data regarding the correlation between MIC and clinical susceptibility to voriconazole are available[15]). All C albicans, C parapsilosis, and C glabrata isolates are susceptible to fluconazole, and all C glabrata isolates are susceptible dose dependent (SDD) to fluconazole. Seventy-seven (76.23%) C albicans isolates are susceptible to voriconazole, whereas 24 (23.77%) isolates are SDD. Nine (64.28%) C parapsilosis isolates are susceptible, and 5 (35.72%) isolates are SDD to voriconazole. Ten (90.90%) voriconazole-susceptible C krusei isolates were found in this study, whereas 1 (9.1%) isolate was found to be SDD. Eight (88.88%) C tropicalis isolates are susceptible to voriconazole, whereas 1 (11.12%) isolate is SDD.

DISCUSSION

Catheter-associated UTI is a common phenomenon especially in the ICU. Prolonged catheterization and chronic illness, such as diabetes, increase the risk of UTI. Candida spp are one of the opportunistic microorganisms that can colonize urethral catheters. In most cases, this colonization lacks clinical significance; however, complications such as Candida UTI with kidney injury or candidemia may occur, as was described in a study by Kauffman et al[7] on candiduria in hospitalized patients. The study revealed that 1.3% of patients developed candidemia.

It is problematic to distinguish between colonization and UTI. Fever is not a specific sign and is common in many ICU patients because of other infections or noninfectious reasons. Classic symptoms of UTI are often lacking in catherized ICU patients. Therefore, physicians tend to use diagnostic tests, such as urine cultures and urine sediment, that show the presence of leukocytes and yeast cells. As previously noted, leukocyturia is not a specific sign of UTI in catherized patients.[17]

In this study, data regarding the prevalence of candiduria in adult catherized in-patients between 2011 and 2013 was gathered. Of the 1,408 patients included in this study, 749 patients had a positive urine culture, and in 146 cases Candida was identified.

In many previous studies, E. coli was the most prevalent microorganism isolated from catherized patients’ urine samples. In our study, Candida was the second most common isolation, whereas previous studies showed Enterococcus spp. As in other studies, C albicans is the most common Candida spp identified in this study.[18,19]

Diabetes mellitus and antibiotic therapy are the common risk factors in this study. Diabetes mellitus was a statistically significant risk factor in C albicans colonized patients (P = .0097) and not in nonalbicans Candida. Malignancy and immunosuppression are additional notable risk factors. Candida was observed in the urine sediment of 28% of the patients, and leukocyturia was observed in 32% of them. These tests are not recommended to diagnose cather-associated candiduria as previously mentioned.

The possible medical interventions in cases of candiduria are diverse, such as cather removal, cather replacement, repeated urine culture, and even antifungal therapy, which is problematic because of side effects, especially with amphotericin B.

One important finding in this study is the inconsistency in dealing with Candida in a urine sample from catherized patients. Only in 29% of cases was the cather removed, as opposed to 63% of cases where no intervention was done; however, some studies and current guidelines recommend the removal or replacement of the cather. Antifungal medications were provided to 3.5% of the patients. This indicates the careful and judicious use of antifungal agents by physicians.

None of the patients in this study developed candidemia, which verifies the relatively low risk of the finding of candiduria in catherized patients.

A high figure of repeated through-cather urine culture was observed in this study (17.8% of cases). Because there was formation of biofilm inside the cather, most if not all repeated cultures were positive for Candida. This highlights the wasteful use of diagnostic laboratory tests.

Table 3
Interventions carried out in patients with candiduria

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>93 (63.69)</td>
</tr>
<tr>
<td>Catheter removal</td>
<td>24 (16.43)</td>
</tr>
<tr>
<td>Repeated culture and cather removal</td>
<td>14 (9.58)</td>
</tr>
<tr>
<td>Repeated culture</td>
<td>10 (6.84)</td>
</tr>
<tr>
<td>Catheter removal and antifungal medication</td>
<td>3 (2.05)</td>
</tr>
<tr>
<td>Catheter removal, repeated culture and antifungal medication</td>
<td>2 (1.36)</td>
</tr>
</tbody>
</table>

**Fig 1.** Mean minimal inhibitory concentration of antifungal agents.
Prevention of systemic Candida infection in patients with fungal colonization by administration of preemptive antifungal therapy has been studied. In our study there was no case of invasive Candida infection, even in immunosuppressed patients, suggesting that perhaps there is no need for antifungal treatment in patients with candiduria.

This study shows the great dilemma of physicians regarding the significance of candiduria in catheterized patients and the problems in differentiation between asymptomatic colonization and UTI which should be treated. It also emphasizes the lack of knowledge of the importance of catheter removal-replacement as part of intervention. Antifungal interventions for eradication of candiduria are futile without removal of Foley catheter. Therefore, large clinical trials should be carried out to investigate the prognosis and clinical infection rate of patients with catheter-associated candiduria in patients who received treatment compared with those who did not. Also, correlation between MIC of antifungal agents in urinary isolates and success in eradicating candiduria and correlation with prognosis in such patients should be further studied.

References


Table 4
Mean minimal inhibitory concentration and susceptibility of Candida isolates to antifungal agents

<table>
<thead>
<tr>
<th>Candida spp</th>
<th>n</th>
<th>Antifungal agents</th>
<th>Mean MIC (µg/mL)</th>
<th>MIC breakpoints (µg/mL)</th>
<th>S</th>
<th>SD</th>
<th>R</th>
<th>IE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Candida spp</td>
<td>146</td>
<td>Amphotericin B</td>
<td>0.260</td>
<td>1</td>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.241</td>
<td>2</td>
<td>64</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.109</td>
<td>0.125</td>
<td>2</td>
<td>104 (71.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>101</td>
<td>Amphotericin B</td>
<td>0.205</td>
<td>1</td>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.25</td>
<td>2</td>
<td>8</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.11</td>
<td>0.125</td>
<td>1</td>
<td>77 (76.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-C. albicans</td>
<td>45</td>
<td>Amphotericin B</td>
<td>0.411</td>
<td>1</td>
<td>1</td>
<td>42 (93.33)</td>
<td>0 (0)</td>
<td>3 (6.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.22</td>
<td>2</td>
<td>64</td>
<td>27 (70)</td>
<td>11 (24.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.106</td>
<td>0.125</td>
<td>2</td>
<td>31 (68.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>14</td>
<td>Amphotericin B</td>
<td>0.452</td>
<td>1</td>
<td>1</td>
<td>13 (92.85)</td>
<td>1 (7.15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.24</td>
<td>2</td>
<td>8</td>
<td>14 (100)</td>
<td>1 (7.15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.108</td>
<td>0.125</td>
<td>1</td>
<td>9 (64.29)</td>
<td>5 (35.71)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>C. krusei*</td>
<td>11</td>
<td>Amphotericin B</td>
<td>0.205</td>
<td>1</td>
<td>1</td>
<td>11 (100)</td>
<td>1 (7.15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.299</td>
<td>2</td>
<td>64</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>11 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.114</td>
<td>0.5</td>
<td>2</td>
<td>10 (90.90)</td>
<td>1 (9.10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>9</td>
<td>Amphotericin B</td>
<td>0.167</td>
<td>1</td>
<td>1</td>
<td>9 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.1</td>
<td>2</td>
<td>8</td>
<td>9 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.099</td>
<td>0.125</td>
<td>1</td>
<td>8 (88.89)</td>
<td>1 (11.12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>7</td>
<td>Amphotericin B</td>
<td>0.895</td>
<td>1</td>
<td>1</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>2 (28.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.211</td>
<td>32</td>
<td>64</td>
<td>0 (0)</td>
<td>7 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.118</td>
<td>1E</td>
<td>1E</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other Candida spp</td>
<td>4</td>
<td>Amphotericin B</td>
<td>0.294</td>
<td>1</td>
<td>1</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>0.22</td>
<td>2</td>
<td>8</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>0.074</td>
<td>0.125</td>
<td>1</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Fluconazole MIC values for C. krusei are not set because it is considered to be intrinsically resistant to fluconazole.

SDD, susceptible do dependent; S, susceptible; R, resistant; NA, not applicable; IE, insufficient evidence; MIC, minimal inhibitory concentration.