American Journal of Infection Control xxx (2015) e1-e4

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

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

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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.

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.[1]

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*.[2]

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 preexisting diabetes mellitus are other known risk factors for candiduria.[3]

Candiduria has 3 categories of severity: (1) colonization or contamination—asymptomatic (most common presentation[4]), (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. Candiduria is unavoidable in 50% of patients with urethral catheters for >5 days.[5]

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

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Additional information: This study was made as part of the requirements for the degree of Doctor of Medicine by Bar Ilan University, Faculty of Medicine.

Conflicts of interest: None to report.

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http://dx.doi.org/10.1016/j.ajic.2015.03.013

Table 1
Organisms that were specified in all positive urine cultures

Organism	n (%)
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*	4 (2.73)
Pseudomonas	114 (15.22)
Enterococcus	76 (10.15)
Klebsiella	68 (9.08)
Proteus	30 (4.01)
Other	21 (1.49)

Table 2
Clinical features of catheter-associated candiduria

Clinical feature	n (%)
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 (08.90)
Diabetes mellitus	19 (13.01)
Malignancy	9 (06.16)
Candidemia	0 (0)

failure or ascending infection caused by contamination of the urine collection bag).[6]

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

The decision whether to treat catheter-associated candiduria is controversial because candiduria can be a sign of colonization where treatment is not required or upper or lower UTI where treatment is mandatory. Previous studies[10] and current guidelines[11] recommend catheter removal (or replacement) and controlling other risk factors as first-line therapy in asymptomatic colonization. Postcatheterization asymptomatic candiduria 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.[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.

MATERIALS AND METHODS

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.

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-μL 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°C. Significant candiduria was defined as the growth of ≥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°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.[15,16]

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.

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 (80.51%), 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 candiduria.

Table 3
Interventions carried out in patients with candiduria

Intervention	n (%)
No intervention	93 (63.69)
Catheter removal	24 (16.43)
Repeated culture and catheter removal	14 (9.58)
Repeated culture	10 (6.84)
Catheter removal and antifungal medication	3 (2.05)
Catheter removal, repeated culture and antifungal medication	2 (1.36)

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 (0.11 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 (0.11 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.

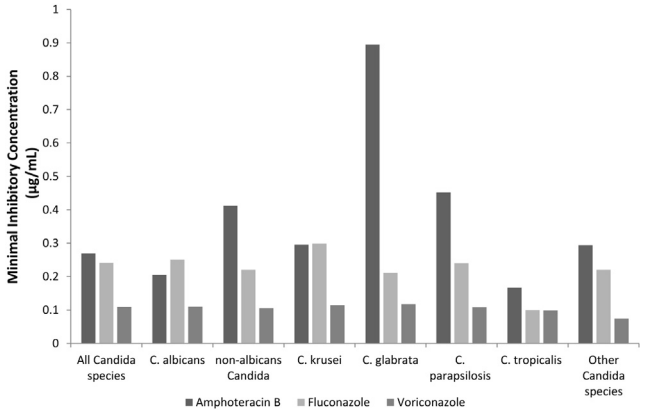

Fig 1. Mean minimal inhibitory concentration of antifungal agents.

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 catheterized ICU patients.[4] 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 catheterized patients.[17]

In this study, data regarding the prevalence of candiduria in adult catheterized 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.

As in many previous studies, *E coli* was the most prevalent microorganism isolated from catheterized 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.[6,18,19]

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 catheter-associated candiduria as previously mentioned.

The possible medical interventions in cases of candiduria are diverse, such as catheter removal, catheter 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 catheterized patients. Only in 29% of cases was the catheter 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 catheter.[11]

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 catheterized patients.

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

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

Candida	n	Antifungal agents	Mean MIC (μg/mL)	MIC breakpoints (μg/mL)		n (%) of isolates			
				S≤	R>	S	SDD	R	IE
All *Candida* spp	146	Amphotericin B	0.269	1	1	143 (97.95)	0 (0)	3 (2.05)	0 (0)
		Fluconazole	0.241	2	64	128 (87.67)	7 (4.79)	0 (0)	0 (0)
		Voriconazole	0.109	0.125	2	104 (71.23)	31 (21.23)	0 (0)	7 (4.79)
C albicans	101	Amphotericin B	0.205	1	1	101 (100)	0 (0)	0 (0)	0 (0)
		Fluconazole	0.25	2	8	101 (100)	0 (0)	0 (0)	0 (0)
		Voriconazole	0.11	0.125	1	77 (76.23)	24 (23.77)	0 (0)	0 (0)
Non-*C albicans*	45	Amphotericin B	0.412	1	1	42 (93.33)	0 (0)	3 (6.66)	0 (0)
		Fluconazole	0.22	2	64	27 (60)	7 (15.55)	11 (24.44)	0 (0)
		Voriconazole	0.106	0.125	2	31 (68.88)	7 (15.55)	0 (0)	7 (15.55)
C parapsilosis	14	Amphotericin B	0.452	1	1	13 (92.85)	0 (0)	1 (7.15)	0 (0)
		Fluconazole	0.24	2	8	14 (100)	0 (0)	0 (0)	0 (0)
		Voriconazole	0.108	0.125	1	9 (64.28)	5 (35.72)	0 (0)	0 (0)
C krusei[*]	11	Amphotericin B	0.295	1	1	11 (100)	0 (0)	0 (0)	0 (0)
		Fluconazole	0.299	NA	NA	0 (0)	0 (0)	11 (100)	0 (0)
		Voriconazole	0.114	0.5	2	10 (90.90)	1 (9.10)	0 (0)	0 (0)
C tropicalis	9	Amphotericin B	0.167	1	1	9 (100)	0 (0)	0 (0)	0 (0)
		Fluconazole	0.1	2	8	9 (100)	0 (0)	0 (0)	0 (0)
		Voriconazole	0.099	0.125	1	8 (88.88)	1 (11.12)	0 (0)	0 (0)
C glabrata	7	Amphotericin B	0.895	1	1	5 (100)	0 (0)	2 (28.51)	0 (0)
		Fluconazole	0.211	32[†]	64	0 (0)	7 (100)	0 (0)	0 (0)
		Voriconazole	0.118	IE	IE	0 (0)	0 (0)	0 (0)	7 (100)
Other *Candida* spp	4	Amphotericin B	0.294	1	1	4 (100)	0 (0)	0 (0)	0 (0)
		Fluconazole	0.22	2	8	4 (100)	0 (0)	0 (0)	0 (0)
		Voriconazole	0.074	0.125	1	4 (100)	0 (0)	0 (0)	0 (0)

IE, insufficient evidence; *MIC*, minimal inhibitory concentration; NA, not applicable; *R*, resistant; *S*, susceptible; *SDD*, susceptible dose dependent.
NOTE. MIC breakpoints are the CLSI[15] and EUCAST[16] clinical breakpoints. The intermediate category is not listed, and it can be interpreted as the values between the S and R breakpoint.
[*]Fluconazole MIC values for *C krusei* are not set because it is considered to be intrinsically resistant to fluconazole.
[†]All nonresistant *C glabrata* isolates are considered to be SDD.

Prevention of systemic *Candida* infection in patients with fungal colonization by administration of preemptive antifungal therapy has been studied.[13] 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.[20] 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.[20]

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