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ORIGINAL ARTICLE

Candida urinary tract infection and *Candida* species susceptibilities to antifungal agents

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The purpose of this study is to review *Candida* isolation from urine of urinary tract infection (UTI) patients over the recent 3 years at the Kobe University Hospital. We recorded the type of strain, the department where the patient was treated such as the intensive care unit (ICU), and combined isolation of *Candida* with other microorganisms. We investigated *Candida* isolation and susceptibilities to antifungal agents and analyzed the risk factors for combined isolation with other microorganisms. The most frequently isolated *Candida* was *Candida albicans*, which showed good (100%) susceptibilities to 5-fluorocytosine (5-FC) and fluconazole (FLCZ) but not to voriconazole (VRCZ), followed by *C. glabrata*. ICU was the greatest source of *Candida*-positive samples, and the most relevant underlying diseases of ICU patients were pneumonia followed by renal failure and post liver transplantation status. Combined isolation with other bacteria was seen in 27 cases (42.9%) in 2009, 25 (33.3%) in 2010 and 31 (31.3%) in 2011 and comparatively often seen in non-ICU patients. Other *candida*s than *C. albicans* showed significantly decreased susceptibility to FLCZ over these 3 years ($P=0.004$). One hundred (97.1%) of 103 ICU cases were given antibiotics at the time of *Candida* isolation, and the most often used antibiotics were cefazolin or meropenem. In conclusion, *C. albicans* was representatively isolated in *Candida* UTI and showed good susceptibilities to 5-FC, FLCZ and VRCZ, but other *candida*s than *C. albicans* showed significantly decreased susceptibility to FLCZ in the change of these 3 years.
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INTRODUCTION

The Infectious Diseases Society of America (IDSA) guideline was established in 2009 and it needs to evaluate the current trends of *Candida* urinary tract infection (UTI).[1–3] Several researchers have stated that *Candida* infections basically emerge only in immune-compromised hosts with dosing such as steroids, immune suppressants or chemotherapy.[2,4,5] However, other authors have found that while immune-compromised status is a risk factor for *Candida* infection, the patients with normal immune states may have a *Candida* infection, and culture tests should include those for fungus.[6–9] In the absence of colonization, disseminated candidiasis is unlikely regardless of the presence of predisposing factors.[7]

Urinary tract mycosis may often result from *Candida* UTI because of *Candida*'s frequency of isolation in urine.[1,10,11] In general, *Candida albicans* is most often isolated in urine followed by *C. glabrata* or *C. tropicallis*. These strains show different trends in pathogenicity[10,12,13] and combined isolation with other microorganisms.[12] The detection of potential risk factors for *Candida* isolation are of clinical importance for understanding their extent of severities and for consideration of treatments, and *Candida* colonization may be considered as the factors for *Candida* infection.[14–16]

Regarding treatments for *Candida*, several established antifungal agents are commercially available.[11,17–19] These drugs are classified based on their targeting points.[20,21] *Candida* susceptibilities to several antifungal agents may be decreasing according to recent trends.[22,23]

In this study, we reviewed the recent cases of *Candida* isolation from urine from UTI patients and *Candida* susceptibilities to antifungal agents over the last 3 years at the Kobe University Hospital, Kobe, Japan.

RESULTS

Candida isolation

Urinary tract *Candida* spp. was isolated over the last 3 years as shown in Table 1. *C. albicans* was the most often isolated strain in all 3 years, followed by *C. glabrata*. *Candida* spp. was the most often isolated from intensive care unit (ICU) patients followed by the urological and general surgery departments (Table 1). Details of patients' backgrounds of ICU cases and their antibiotic uses before *Candida* isolation were shown in Tables 2 and 3. Shortly, the most relevant underlying diseases of ICU patients were pneumonia followed by renal failure or post-liver transplantation status. One hundred (97.1%) out of 103 ICU cases were given antibiotics at the time of *Candida* isolation, and the median duration of antibiotics usage

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Table 1 Patients' backgrounds

	2009	*2010*	*2011*
n	*63*	*75*	*99*
Inpatients department	59 (93.7%)	70 (93.3%)	89 (89.9%)
ICU	34	28	41
Urology	7	5	5
General surgeons	3	4	6
Gynecology	2	6	4
Cardiovascular	0	5	3
Digestive diseases	1	5	2
Others	12	17	28
Outpatients	4 (6.3%)	5 (6.7%)	10 (10.1%)

Abbreviation: ICU, intensive care unit.

Table 2 Details of ICU patients' backgrounds

n	*103*
Gender	
Male	42
Female	61
Underlying diseases	
Pneumonia	30
Renal failure	5
Post liver transplantation status	4
Aortic aneurysm	4
Cerebral hemorrhage	4
Heart failure	4
Burns	3
Others	49

Table 3 Antibiotics use before *Candida* isolation of ICU patients

Frequently used antibiotics	n
Cefazolin	35
Meropenem	35
Vancomycin	13
Doripenem	11
Pazufloxacin	11
Sulbactam/ampicillin	11
Tazobactam/piperacillin	10
Cefozopran	9
Clindamycin	6
Imipenem	5
Cefpirome	8
Minocycline	4
Others	25
Antibiotic duration (days)	
Use	100 (97.1%)
1∼5	30
6∼10	23
11∼20	31
21∼	16
Non-use	3 (2.9%)

Table 4 Combined isolation of *Candida* spp. with other microorganisms

	2009	*2010*	*2011*
n	*63*	*75*	*99*
Single culture	36 (57.1%)	50 (66.7%)	68 (68.7%)
ICU	24 (66.7%)	23 (46.0%)	37 (54.4%)
Non-ICU	12 (33.3%)	27 (54.0%)	31 (45.6%)
Organism			
C. albicans	21 (58.3%)	28 (56.0%)	35 (51.5%)
C. glabrata	7 (19.4%)	11 (22.0%)	25 (36.8%)
C. parapsilosis	5 (13.9%)	8 (16.0%)	2 (2.9%)
C. tropicalis	3 (8.3%)	3 (6.0%)	4 (5.9%)
C. guilliermondii	0	0	2 (2.9%)
Multiple cultures	27 (42.9%)	25 (33.3%)	31 (31.3%)
ICU	10 (37.0%)	5 (20.0%)	4 (12.9%)
Non-ICU	17 (63.0%)	20 (80.0%)	27 (87.1%)
Kinds			
Two kinds	17 (63.0%)	18 (72.0%)	20 (64.5%)
Three kinds	9 (33.3%)	5 (20.0%)	8 (25.8%)
Four kinds	1 (3.7%)	1 (4.0%)	2 (4.9%)
> Five kinds	0	1 (4.0%)	1 (2.4%)
Organism			
C. albicans	21 (29.4%)	15 (45.5%)	24 (58.5%)
C. glabrata	6 (17.6%)	12 (36.4%)	14 (34.1%)
C. parapsilosis	1 (2.9%)	3 (9.1%)	2 (4.9%)
C. tropicalis	6 (17.6%)	3 (9.1%)	1 (2.4%)
C. guilliermondii	0	0	0

Abbreviation: ICU, intensive care unit.

Table 5 Antifungal susceptibility (%) of *Candida* spp

Organism/antifungal	*2009*	*2010*	*2011*	*r*	*p*	*b*
C. albicans						
Tested number of isolates	37	35	52			
5-FC[a]	100	100	100	—	—	—
FLCZ	100	100	96.2	0.866	0.333	−0.395
ITCZ	40.5	31.4	48.1	0.454	0.700	0.054
VRCZ	100	100	100	—	—	—
Non C. albicans[a]						
Tested number of isolates	21	33	46			
5-FC	100	100	100	—	—	—
FLCZ	47.6	33.3	15.2	0.998	0.004	−0.061
ITCZ	100	100	100	—	—	—
VRCZ	90.5	87.9	89.1	0.538	0.638	−0.413

Abbreviations: 5-FC, 5-fluorocytosine; FLCZ, fluconazole; ITCZ, itraconazole; VRCZ, voriconazole.
r, correlation coefficient and b, regression coefficient.
[a]*C. glabrata*, *C. parapsilosis* and *C. tropicali.*

was 10 days before *Candida* isolation. The median number of used antibiotics was two antibiotics and the most often used antibiotics were cefazolin and meropenem followed by vancomycin.

Our investigation of combined isolation with other microorganisms showed that 27 cases (42.9%) of isolated *Candida* in 2009, 25 (33.3%) in 2010 and 31 (31.3%) in 2011 had combined isolation with

other microorganisms (Table 4). Non-ICU patients tended more likely to have combined isolation (two or more kinds of *Candida* or combined isolation with other microorganisms) (63.0% in 2009, 80.0% in 2010 and 87.1% in 2011). *C. albicans* was also the most frequently isolated in this context as well (61.8% in 2009, 45.5% in 2010 and 58.5% in 2011) followed by *C. glabrata* (17.6% in 2009, 36.4% in 2010 and 34.1% in 2011). The microorganisms most commonly isolated in combination with *Candida*s were *Enterococcus faecium*, *Pseudomonas aeruginosa* or *Enterococcus faecalis*.

Susceptibilities to antifungal agents

We analyzed the data on *Candida* susceptibilities to representative antifungal agents. The data showed that over these 3 years *C. albicans* had good susceptibilities to 5-fluorocytosine (5-FC), fluconazole (FLCZ) and voriconazole (VRCZ); the susceptibility ratio was comparatively good (96.2 to 100%) (Table 5). Other *Candida*s (*C. glabrata*, *C. parapsilosis* and *C. tropicalis*) had good susceptibilities to 5-FC and itraconazole (ITCZ) (100%), whereas susceptibility to FLCZ have become significantly lower ($P = 0.004$) in the change of these 3 years investigated.

DISCUSSION

UTIs have been the focus of numerous studies, including optimal antibiotic treatments, the utility of urinary tract drainage, changes in causative microorganisms over time and in different regions and UTI categorization, such as complicated or uncomplicated UTI.[11,24] This study focused on urinary tract mycosis, particularly *Candida,* which is comparatively often isolated from urine.[1,11,25] We found that *C. albicans* and *C. glabrata* dominated our isolation of *Candida* from urine, representing about 90% of all the *Candida* cultured from our urine samples, and this high prevalence ratio is similar to that in other studies.[10,12,13]

Many cases involve multiple isolations with other microorganisms and *Candida*-related infections are also associated with immune-compromised patients.[1,11] Immune-compromised patients easily become infected with mixed pathogenic microorganisms.[1] Fisher *et al.*[26] reported that *C. albicans*, compared with other *Candida* spp. such as *C. glabrata*, have the potential for strong adhesion, and this may be one reason for mixed infection or isolation with other microorganisms. The risks for these mixed isolations were reported by Sobel *et al.*,[12] who found that more than one species of *Candida* were found simultaneously in over 10% of patients, and candiduria frequently coexists with or follows bacteriuria.

Our data showed that mixed isolation (two or more kinds of *Candida* isolated or combined isolation with other microorganisms) tended to be seen more often in non-ICU patients. In general in our medical system, ICU patients are in a hyper-acute phase or status, so the duration of hospitalization or medical interventions in most cases is shorter than for non-ICU patients, a category that includes the cases with long-hospital admission and associated hospital exposure. In addition, our data showed pneumonia, renal failure and post liver transplantation status were often seen in ICU cases and most of them (97.1%) were given antibiotics before *Candida* isolation. Fischer *et al.*[27] revealed that the important risk factors for severe fungal infection were frequent or long-term medical exposure or treatments such as antibiotic dosing. Lundstrom and Sobel[11] thought it is likely that antibiotics contribute to colonization by *Candida* spp. by suppressing endogenous bacterial flora. These works support our results and these kinds of studies need to be followed up in our medical system; debate persists on whether the *Candida* was isolated from UTI or colonization. Some authors have concluded that *Candida* isolation from urine is mostly due to medical devices such as urinary tract catheters and should be regarded as colonization in most cases,[25,28,29] requiring no treatments. Others conclude that *Candida* colonization is a definitive risk factor for *Candida* infections and these are often severe in immune-compromised hosts, including those undergoing chemotherapy or other immune-suppressant treatments, and in such cases *Candida* needs to be treated.[1,2,11] We suggest, considering our results of severity especially in ICU-patients shown in Table 2, that the treatments in immune-compromised cases may be necessary like the latter opinions.

As to the susceptibilities to antifungal agents, our data showed that all our tested *Candida* spp. (*C. albicans*, *C. glabrata*, *C. parapsilosis* and *C. tropicalis*) had good susceptibilities to 5-FC, but other *Candida* than *C. albicans* showed decreased susceptibilities to FLCZ. These results were similar to those of Schmalreck *et al.*[23] who also reported decreased susceptibilities to FLCZ and VRCZ in *C. glabrata* and *C. tropicalis*, respectively. They also reported that a decreased susceptibility to 5-FC was found in *C. tropicalis*. Pemán *et al.*[30] showed that *Candida* spp. were all susceptible to 5-FC and VRCZ, but *C. glabrata* and *C. krusei* had decreased susceptibilities to these anti-fungal agents. Further, FLCZ failures of the treatment of *C. glabrata* causing renal infection have been reported with increasing frequency.[31]

We would like to emphasize the limitations of this study. First, this study is retrospective and includes all the urine materials isolated regardless of infection or colonization. Next, the number of *Candida* cases may not be enough for definitive conclusions, however, these are the consecutive cases of our institution. Third, the patients' backgrounds were investigated only from ICU patients partly because those of non-ICU patients had wide range of variation and were considered difficult to be analyzed. These limitations should be resolved in our future investigation of urinary tract *Candida*.

In conclusion, we documented urinary tract *Candida* isolation and combined isolation with other microorganisms and found that the latter tended to be seen more commonly in non-ICU patients. Other *Candidas* than *C. albicans* showed decreasing susceptibility to FLCZ in the change of these 3 years (2009–2011). Further approaches to address *Candida* infection will be based on this baseline study evaluating urinary tract *Candida* institutionally.

METHODS

Patients

Fungus was isolated from urine specimens from patients with UTI patients from January 2009 to December 2011 in Kobe University Hospital. We investigated the susceptibilities of isolated fungi to representative antifungal agents. UTI was defined as a symptomatic fungus isolation of 10^5 or more colony forming units per ml in urine. We recorded the patient's sex, type of strain, departments treating the patient, combined isolation with other microorganisms and analyzed the patients especially focusing on the categorization of ICU or non-ICU patients and antibiotics usage before *Candida* isolation in ICU patients.

Susceptibility testing

Antifungal agents' susceptibilities were tested and the results were interpreted and reported using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M27-S3 (2008. CLSI Document M100-S20). The MIC was defined as the lowest antimicrobial concentration that totally inhibited bacterial growth. Susceptibilities were evaluated by CLSI category. We tested *Candida* strains against the following antifungal agents by using drug susceptibility tests kit for yeast-like fungus (ASTY) (Kyokuto Pharmaceutical Industrial Co, Ltd, Takahagi, Japan) after 48 h of cultures: 5-FC, FLCZ, ITCZ and VRCZ. For quality control, *C. parapsilosis* ATCC22019 or *C. Krusei* ATCC6258 were used.

Statistical analyses

Statistical analysis was conducted using linear regression analysis with PASW Statistics 17.0 software packages (for Windows; SPSS Inc., Chicago, IL, USA). The *Candida* susceptibilities of isolated strains to antifungal agents treatments were analyzed with linear regression analysis. Statistical significance was established at the 0.05 level.

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