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ORIGINAL ARTICLE

Performance of yeast-like cell counting (YLCC) using the Sysmex UF-1000i for clinical candiduria screening

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Abstract

Candiduria is common in clinical practice. However, an effective and convenient assay to screen for candiduria is still needed. This study aimed to evaluate the performance of the Sysmex UF-1000i urine analyzer for yeast-like cell counting (YLCC) to screen for candiduria prior to urine culture. We retrospectively analyzed data from 5233 urine samples from 1813 patients, including 837 males and 976 females. Urine culture and urinalysis-obtained YLCC data were used to estimate the performance of YLCC in diagnosing candiduria. Different cutoff values were used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The YLCC-positive rates differed according to the Candida colony-forming units (CFU) counts in the urine samples. A sharp drop in YLCC-positive rate (from 64.3 to 22.0%) was observed between the urine groups with 10^4 CFUs and 10^3 CFUs. A cutoff value of 0 YLCs/μL results in the highest Youden index (0.71) with 77.04% sensitivity and 93.68% specificity. In a group of 34 hospitalized candiduria patients with serial urinalysis data, 25 were YLCC-positive before urine culture. In conclusion, YLCC with the Sysmax UF-1000i could serve as an auxiliary technique to exclude culture-negative specimens prior to urine culture. Positive YLCC results could imply candiduria, especially when persistent YLCC-positive results were observed.

Keywords Candiduria · Yeast-like cell · Sysmex UF-1000i · Urinalysis · Cutoff value · Fungal urinary tract infection

Introduction

"Candiduria" refers to the presence of Candida yeasts in urine, which is one of the most common conditions encountered in clinical practice [1, 2]. According to reports, candiduria cases have dramatically increased over the past 30 years [3, 4]. In most cases, patients with candiduria do not have symptoms of a UTI, and antifungal therapy is not essential. However, several studies have shown an association between candiduria and high-risk Candida infections, such as candidemia, for which therapeutic intervention should be seriously considered [5]. Urine culture is the primary method to identify candiduria in clinical laboratories. However, microbiological culture is labor-intensive and time-consuming, and a simple method for candiduria identification is urgently needed [6].

Previous studies have implied the reliability of the automatic analysis system UF-1000i for the detection of bacteria and yeast-like cells (YLCs) in urine [7–9]. The Sysmex UF-1000i system can efficiently measure each detected formed element (including fungi) in urine, potentially meeting the demands of rapid candiduria screening in large clinical populations. In the present study, we retrospectively analyze the data from urine culture and routine urinalysis performed using the UF-1000i in our hospital. The objective of this study is to evaluate the performance of YLC counting (YLCC) on screening for candiduria prior to urine culture.

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Materials and methods

Study design and subjects

We investigated data from 5233 urine samples from 1813 patients, including 837 males and 976 females. The enrolled patients' age ranged from 8 days to 106 years with a median

Table 1 Bacterial and *Candida* strains isolated from culture-positive urine samples

Bacteria/*Candida*	No. of strains	Percentage (%)
Gram-negative bacillus	1397	50.1
Escherichia coli	653	23.4
Klebsiella spp.	226	8.1
Proteus spp.	193	6.9
Pseudomonas spp.	153	5.5
Acinetobacter spp.	96	3.4
Others	76	2.7
Gram-positive bacterium	1044	37.4
Enterococcus faecium	384	13.8
Enterococcus faecalis	352	12.6
Staphylococcus epidermis	218	7.8
Streptococcus agalactiae	38	1.4
Staphylococcus aureus	35	1.3
Others	17	0.6
Candida spp.	347	12.4
Candida albicans	169	6.1
Candida tropicalis	67	2.4
Candida glabrata	49	1.8
Candida parapsilosis	43	1.5
Candida krusei	13	0.5
Others	6	0.2

age of 62. The investigation started on January 1, 2016, and ended on August 31, 2017.

The patients were instructed on how to collect middle-stream urine prior to sample collection. For babies younger than 1 year, a sterile urine collection bag was applied. All flow analyses were performed in an ISO 9000-accredited laboratory. Approximately 4 mL of urine is needed for analysis.

Microbiological analysis

Ten microliters of each urine sample was directly spread onto CHROMagar™ agar plates, and the culture plates were incubated aerobically at 37 °C for 24–48 h. Positive cultures were identified according to colony morphology and confirmed using biochemical reactions referenced in Bergey's Manual of Systemic Bacteriology. Urine samples with bacterium or yeast growth were recorded as positive. Samples found to have more than two microorganisms were considered contaminated.

Data analysis and statistical methods

Statistical analysis was performed with GraphPad Prism 7.00. Different cutoff values were used to calculate sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV). Differences between YLCC-positive rates among candiduria subgroups were compared using the chi-squared test. Consistency between the urine culture and YLCC was determined using the kappa (κ) coefficient. $P < 0.05$ was considered significant.

Results

Of the 5233 urine samples investigated, 47.05% were culture-positive. Two thousand four hundred forty-one strains of bacterium and 347 strains of Candida spp. pathogens were isolated. As Table 1 indicates, gram-negative bacteria, gram-positive bacteria, and Candida spp. accounted for 50.1%, 37.4%, and 12.4%, respectively, of the urinary pathogens. *Candida albicans* was the major Candida spp. pathogen isolated from urine (6.1%).

Patients without a urinalysis and a urine culture performed on the same day were excluded. Therefore, of the 347 candiduria episodes, 268 were validated for further investigation. The candiduria episodes were divided into 5 subgroups according to their colony-forming unit (CFU) counts. As Table 2 shows, in the CFU > 10^5/mL subgroup, the YLCC-positive rate was 82.8% with a medium YLCC of 223.1/μL (ranging from 1.8/μL to 18,579.7/μL). When the CFU counts dropped to 10^5, 10^4, 10^3, and < 10^3/mL, the positive rates were respectively decreased to 71.9%, 64.3%, 22.0%, and 18.2%. The result of the chi-squared test indicated that the positive rates were significantly different among the subgroups ($P < 0.001$). A sharp drop in YLCC-positive rate was observed between the subgroups containing 10^4 and 10^3 CFUs.

Table 2 Yeast-like cell counts for the 268 urine samples from candiduria patients

CFU count (/mL)	YLCC-positive (*n*)	YLCC-negative (*n*)	Positive %[a]	Medium YLCC (/μL) (range)
> 100,000	101	21	82.8	223.1 (1.8–18,579.7)
100,000	23	9	71.9	146.9 (3.8–3500.1)
10,000	27	15	64.3	77.4 (3.8–3921.0)
1000	11	39	22.0	171.5 (18.8–1674.1)
< 1000	4	18	18.2	56.5 (3.2–159.7)

CFU, colony-forming units of Candida cells, *YLCC* yeast-like cell count

[a] Positive % = $n_{\text{YLCC-positive}}/(n_{\text{YLCC-positive}} + n_{\text{YLCC-negative}}) \times 100\%$

Table 3 Diagnostic performance of YLCC cutoff values on candiduria screening

Cutoff (YLCs/μL)	SE (%)	SP (%)	PPV (%)	NPV (%)	Youden index[a]
0	77.04	93.68	40.48	98.65	0.71
15.2	71.94	94.76	43.38	98.37	0.67
50	55.61	96.10	44.31	97.49	0.52
100	46.43	97.27	48.66	97.02	0.44

SE sensitivity, *SP* specificity *PPV* positive predictive value, *NPV* negative predictive value

[a] Youden index was defined as $J(t)$ = sensitivity + specificity − 1

For the validated 1867 aseptic and 1571 bacteriuria samples, the YLCC-positive rate was 5.03% (94/1867, ranging from 2.4 to 1597.7/μL) and 7.19% (113/1571, ranging from 1.4 to 3775.6/μL), respectively.

SE, SP, PPV, and NPV were assessed and are shown in Table 3. As the cutoff value increased from 0 to 15.2, 50, and 100 YLCC/μL [9–11], the SP increased from 93.68 to 97.27%, and the PPV increased from 40.48 to 48.66%. However, the SE declined from 77.04 to 46.43% and the NPV declined from 98.65 to 97.02%. The Youden index was calculated to indicate the accuracy of YLC detection and offer an optimal cutoff value. In the present study, the highest Youden index was 0.71 at a cutoff value of 0 YLCC/μL.

Urine culture detected 196 Candida-positive samples and 3510 Candida-negative samples of the 3706 specimens, while 151 samples tested Candida-positive and 3288 tested Candida-negative both in YLCC and urine culture. In addition, YLCC gave positive results for 222 culture-negative samples and negative results for 45 culture-positive samples. A moderate consistency (kappa = 0.496) was observed between the urine culture and YLCC (Table 4).

In a group of 34 hospitalized candiduria patients, the availability of serial routine urinalysis data allowed us to study the dynamic change in YLCCs. In 25 patients, YLCCs were positive before the candiduria was confirmed by urine culture. Interestingly, the kinetics of changes in YLCCs showed a constant rise at the approximate time of clinical and microbiological evidence of candiduria existence and then dropped if the patient responded to antifungal therapy. The kinetics of YLCC in a patient with confirmed candiduria are shown in Fig. 1.

Table 4 Results of Sysmex UF-1000i YLCC and clinical urine culture

		YLCC		
		Positive	Negative	Total
Urine culture	Positive	151	45	196
	Negative	222	3288	3510
	Total	373	3333	3706

YLCC compared to urine culture, kappa = 0.496

Discussion

Candiduria is common in the clinic. In this study, 12.4% of the microbial pathogens isolated from urine were Candida spp. Since urine culture is not convenient, researchers have begun to explore the possibility of YLC detection in candiduria identification. Recent results presented by Le et al. [10] showed that when an appropriate YLCC cutoff value was chosen, the odds that the patient had a fungal UTI were as high as 90%. The present study retrospectively analyzed the results of urine culture and UF-1000i analysis in our hospital, which could provide unique perspectives on the efficiency of YLCC in candiduria screening.

In the 268 positive urine culture episodes, the YLCC-positive rate was 61.9%. Interestingly, we observed an association between urine Candida CFU counts and YLCC-positive rates, and a great YLCC-positive rate gap existed between the urine subgroups containing 10^3 and 10^4 CFUs (from 22.0 to 64.3%). The standard CFU value used for confirming candiduria in urine culture varies in different laboratories, usually from 10^3 to 10^5 CFU/mL [12–14]. Our results suggest that YLCC using the Sysmax UF-1000i is more suitable for identifying urines with relatively high Candida concentrations. We recommend using a culture standard of 10^4 CFU/mL for candiduria determination by YLCC screening.

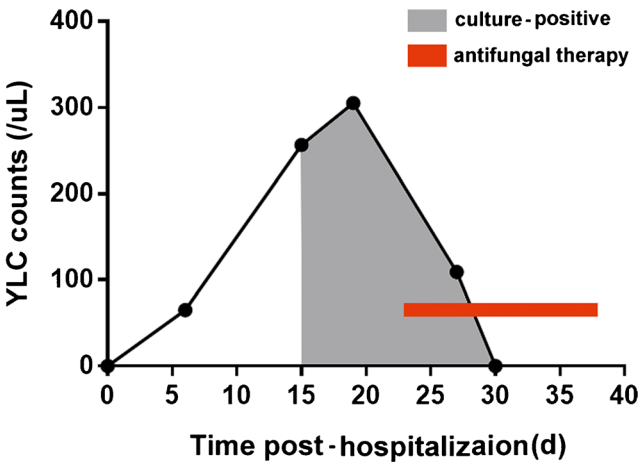

Fig. 1 Kinetics of YLCCs for a typical candiduria patient with serial urinalysis. The gray area indicates the days in which the urine cultures yielded *Candida albicans*. The red bar shows the days during which the patient was treated with fluconazole

Our data indicate that a cutoff value of 0 YLCs/μL results in the highest Youden index. The SE, SP, PPV, and NPV of YLCCs for candiduria screening are similar to the results reported by previous studies [9, 10]. The three studies have a common characteristic that the NPVs were very high while the PPVs were low, even when using appropriate cutoff values. The reasons for the low PPVs might be (1) low prevalence of significant candiduria in the study populations [15, 16]; (2) confusion caused by other urine sediment particles, especially RBCs with YLCs, leading to false positives [11]; and (3) use of antifungal therapy, which would result in low yeast loads, leading to false negatives. We observed a moderate correlation between urine culture and YLCC in this study. High NPV and moderate correlation with urine culture suggest that YLCC is valuable for identifying patients without candiduria.

YLCCs constantly rose in association with the clinical and microbiological diagnosis of urinary Candida infection and decreased and eventually vanished if the patient responded to antifungal therapy. The reason for this is that, in clinical practice, urine culture is warranted only when the patient exhibits urinary tract infection symptoms, while yeast or bacteria are present in the urine prior to the onset of UTI symptoms. Additionally, there is a time gap between urinalysis and urine culture because a urine culture takes several days to grow. Bacteria and leukocyte counting based on UF-1000i urinalysis is successful in the prediction of urine culture growth and initiates ordering of a urine culture or starting antibiotic therapy, if a bacterial UTI is suspected [17–19]. Our kinetic data suggest that a candiduria diagnosis is expected if the YLCC is consistently positive, especially when it is rising steadily.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval and informed consent Ethical approval was obtained from the Ethics Review Board of Bethune International Peace Hospital (2016-KY-034). The need for individual patient informed consent was waived for this retrospective study.

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