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Factors accounting for misidentification of *Candida* species

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From April 15 through June 15, 1999, a total of 660 yeast isolates were collected from 22 hospitals in Taiwan to investigate factors determining the accuracy of yeast identification. The germ tube test was the method most frequently used by hospitals for yeast identification, followed by the API-32C, cornmeal agar window test, and assimilation method. All of the submitted isolates were re-speciated in the National Health Research Institutes laboratory. The frequencies of inconsistent identification of isolates between hospitals and the National Health Research Institutes laboratory varied with the location and the type of hospital. The sensitivity and specificity of the germ tube test were 95% and 98.6%, respectively. This study showed that hospitals using the germ tube test as the first step in yeast identification had fewer inconsistent identifications of isolates than those using other methods. The VITEK Yeast Biochemical Card and API-32C had a sensitivity of 92.6% and 98.3%, respectively. No single method consistently identified all yeast isolates. Thus, every laboratory should have at least 2 methods available for yeast identification.

Key words: *Candida* species, germ tube test, identification

The number of nosocomial yeast infections has increased in the past decade. In the United States, yeast infections ranked fourth among the most common cause of nosocomial bloodstream infection [1,2]. In Taiwan, the prevalence of nosocomial candidemia increased 27-fold from 1981 through 1993 [3,4].

The increasing prevalence of yeast infections highlights the need for simple and rapid methods to identify clinically important yeast in microbiological laboratories. *Candida* species have various degrees of susceptibility to different antifungal agents. *Candida krusei* and *Candida glabrata* are less susceptible to fluconazole than other *Candida* species [5,6], and *Candida lusitaniae* is relatively resistant to amphotericin B [7]. The accurate identification to the species level and susceptibility testing are thus crucial for clinical management. The yeast survey performed by the College of American Pathologists in 1999 showed that only 84.4%, 54.1%, and 59.8% of 590 participants identified *Candida albicans*, *Candida parapsilosis*, and *Candida tropicalis*, respectively, to the species level [8]. The aim of this study was to investigate the distribution of clinical yeast isolates and factors determining the accuracy of yeast identification in Taiwan.

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Materials and Methods

Organisms and media

Yeast isolates were collected from 22 hospitals in Taiwan. Each hospital was asked to submit 10 *C. albicans* and 40 non-*albicans Candida* spp. isolates during the collection period from April 15 through June 15, 1999. Only 1 isolate was accepted for each episode of infection. Isolates were stored frozen at -70°C in beads containing Microbank cryovials (PRO-LAB Diagnostics, Austin, TX, US). At the end of the collection period, isolates were kept frozen and transported by an express delivery company to the National Health Research Institutes (NHRI) laboratory within 24 h. The isolates were first subcultured on Sabouraud dextrose agar (SDA; BBL, Becton Dickinson, Cockeysville, MD, US) to check for purity and identification. Pure isolates were labeled and stored in vials that contain 50% glycerol at -70°C for further analysis.

Identification

In the NHRI laboratory, all isolates were first subjected to the germ tube test of 10% goat serum (GibcoBRL 16210-064, Grand Island, NY, US) in brain heart infusion (BHI; BBL) medium at 37°C for 2 to 3 h [9, 10]. The VITEK Yeast Biochemical Card (YBC; bioMerieux, St Louis, MO, US) was used to identify those isolates negative by the germ tube test. API-32C (bioMerieux) was used to confirm the NHRI result when

the VITEK-YBC showed less than 90% positive.

When the identification of an organism was inconsistent between the hospital and the NHRI laboratory, the organism was re-subcultured from the original tube and identified by the VITEK-YBC and API-32C methods simultaneously. Methods used by hospitals and the NHRI laboratory for identification were as follows: germ tube test, API-ID32C, cornmeal agar window test, assimilation method, Mycotube, API-ID20C, VITEK-YBC, and CHROMagar test. Detailed procedures of these methods have been previously described by Forbes *et al* [11]. API-ID systems, VITEK-YBC, Mycotube, and conventional assimilation methods generally employ substrates in determining the utilization profiles of yeasts. The cornmeal agar morphology window test determines if the yeast produces conidia, filaments, and/or chlamydospores to identify the isolates to the species level. The methods used for yeast identification in the NHRI laboratory were the germ tube test, VITEK-YBC, and API-ID32C.

If a hospital identified an organism as a different species compared with the result from the NHRI laboratory, the identifications were considered inconsistent. The frequencies of inconsistent identifications were measured only when participating hospitals performed the identification to the species level. For those isolates with inconsistent identifications, further identifications to the species level by cornmeal agar window test and CHROMagar test were performed.

Database and analysis

The following information of each isolate was logged into the database: hospital origin, location and type of hospital, genus and species as identified by each hospital and the NHRI laboratory, sources of isolates (urine, sputum, blood, wound, and others), whether patients had a hospital-acquired infection, and the procedures for identification. Hospital-acquired infections were identified by the hospital infection control practitioners in their routine surveillance according to the criteria of the Centers for Disease Control and Prevention [12].

Data analysis was performed using Epi Info 6.04 (CDC, Atlanta, GA, US) [13,14]. The significance of differences in frequencies and proportions was determined by the chi-square test with Yates correction.

Results

Distribution of isolates

From April 15 through June 15, 1999, 660 yeast isolates were collected from 22 participating hospitals. Table 1 shows the sources of the isolates. Urine (42.1%) was the most common source of yeast clinical isolates, followed by sputum (22.7%), blood (8.2%), and wound (7.7%). The distribution of *Candida* species in different sources is shown in Table 2. *C. glabrata* was the most common non-*albicans Candida* species isolated from urine (106/199), whereas *C. tropicalis* was the most common non-*albicans Candida* species isolated from sputum (40/68), blood (12/38), and wound (12/31). The distribution of isolates among the medical centers, regional hospitals, and local teaching hospitals is shown in Table 3. Medical centers provided 247 isolates for this study; regional and local teaching hospitals provided 413. On average, medical centers contributed more isolates than non-medical center hospitals (41 vs 26). The mean number of samples was 33 (range, 3-50) per hospital.

Of these 660 isolates, *C. albicans* (242 isolates; 37%) was the most common species, *C. tropicalis* (161; 24%) and *C. glabrata* (155; 23%) were the 2 major non-*albicans* species, followed by *C. parapsilosis* (50; 7.6%), *C. krusei* (10; 1.5%), *Trichosporon beigelii* (10; 1.5%), and other species (32; 5.4%). According to the criteria of the Centers for Disease Control and Prevention, 23.2% (153/660) of the isolates belonged to hospital-acquired infections. The most common species isolated from patients with nosocomial infections were *C. albicans* (45.1%), followed by *C. tropicalis* (22.9%), *C. glabrata* (21.6%), and *C. parapsilosis* (6.5%).

Initial identification by the participating hospitals

Eight different methods for yeast identification were used by the 22 participating hospitals (Table 3). Half of the hospitals used a combination of 2 methods to identify yeast clinical isolates whereas 8 hospitals used a combination of 3 or more methods. Three hospitals used only 1 method. Among the 22 hospitals, 17 used

Table 1. Clinical sources of yeast isolates (n = 660)

Source	No. of isolates (%)
Urine	278 (42.1)
Sputum	150 (22.7)
Blood	54 (8.2)
Wound	51 (7.7)
CVP	13 (2)
Ascites	12 (1.8)
Nail	9 (1.4)
CSF	5 (0.8)
Others	88 (13.3)

Abbreviations: CSF = cerebrospinal fluid; CVP = central venous pressure line

Table 2. Distribution of *Candida* species isolated from different sources

	C. albicans	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	Others	Total
Urine	79	106	7	74	12	278
Sputum	82	19	3	40	6	150
Blood	16	8	12	12	6	54
Wound	19	4	10	12	5	50
Others	46	18	18	23	23	128
Total	242	155	50	161	52	660

the germ tube test as the first step in identifying yeast. Three hospitals used the cornmeal agar window test method, and 2 hospitals used either the API-ID32C or the VITEK-YBC as the first step. The frequency of each method used by the hospitals was as follows: germ tube test, 77.7%; API-ID32C, 45.5%; cornmeal agar window test, 40.9%; assimilation method, 27.3%; Mycotube, 18.2%; API-ID20C, 13.6%; VITEK-YBC, 9%; and CHROMagar test, 4.6%.

Further identification by the National Health Research Institutes laboratory

All submitted isolates were re-identified by the germ tube test, VITEK-YBC, and API-32C methods. Among the 660 isolates, 237 (35.9%) were positive and 423 (64.1%) were negative by the germ tube test. Of those positive isolates, 1 failed to grow at 42°C and was identified as *C. dubliniensis* by the VITEK-YBC and API-32C methods. The hospitals and the NHRI laboratory identified 214 germ tube positive isolates as *C. albicans*. In 16 of 22 isolates with inconsistent identifications, the VITEK-YBC confirmed the result of the NHRI laboratory of *C. albicans*. Both VITEK-YBC and API-32C confirmed the result of the hospitals for the remaining 6 *C. tropicalis* isolates, which were false positive on the germ tube test performed in the NHRI laboratory.

Among the 423 negative isolates by the germ tube

Table 3. Distribution of isolates and frequency of inconsistent identification

Hospital no.	Type	Area	No. of isolates	Consistent	Inconsistent (%)	Methods[a]
1	RH	N	23	22	1 (4.3)	B,D,C
2	RH	N	19	17	2 (10.5)	A,D,F
3	MC	N	50	47	3 (4)	A,C,B
4	RH	N	26	26	0	A,B
5	RH	N	14	12	2 (14.3)	A,D,C
6	MC	N	50	49	1 (2)	A,D,H
7	RH	N	28	23	5 (17.9)	A,D,C,B
8	RH	N	8	7	1 (12.5)	A,B
9	RH	N	20	19	1 (5)	G
10	MC	N	29	29	ND[b]	C,B
11	RH	N	39	39	0	A,E
12	LT	C	50	47	3 (6)	A,E
13	RH	C	50	41	9 (18)	C,E
14	MC	C	29	28	1 (3.4)	A,C,D,G,B
15	RH	S	33	25	8 (24.2)	C,B
16	MC	S	49	42	7 (14.3)	A,B
17	RH	S	29	29	ND[b]	A
18	MC	S	40	40	0	A,B
19	RH	S	20	13	7 (35)	A,E
20	RH	E	23	23	0	A,C,F
21	RH	E	28	28	ND[b]	A
22	LT	E	3	2	1 (33.3)	A,F
Total			660	608	52 (9.1)	

Abbreviations: C = central region; E = eastern region; LT = local teaching hospital; MC = medical centers; N = northern region; ND = not determined; RH = regional hospital; S = southern region

[a]Methods used by hospitals: A = germ tube test; B = API-ID32C; C = cornmeal agar window test; D = assimilation method; E = Mycotube; F = API-ID20C; G = VITEK-YBC; H = CHROMagar test.

[b]Hospitals reported organisms as "Candida species" or "yeast-like".

test, the VITEK-YBC identified 390 isolates, of which 363 were identified consistently by both hospitals and the NHRI laboratory. The API-32C confirmed the result of the NHRI laboratory for the 27 isolates with inconsistent identifications. Of the remaining 33 isolates that the VITEK-YBC failed to identify, the hospitals and the NHRI laboratory identified 24 isolates consistently.

Inconsistency of identification

A total of 58 inconsistent results were found after the first round of yeast identification by the NHRI laboratory. The identifications of 6 isolates confirmed the hospital results by both the VITEK-YBC and API-32C methods. The identification of the other 52 discrepant results confirmed the results of the NHRI laboratory by both the VITEK-YBC and API-32C methods. Table 3 shows the number and frequency of isolates with inconsistent results identified by the NHRI laboratory and hospitals. Because 3 hospitals identified non-*albicans* isolates as either "yeast-like" or "*Candida* species" without further specification, the ability of these laboratories to identify these organisms to species level could not be compared. The frequency of isolates with different identifications among the 19 hospitals and 574 isolates included in this study were then determined. The NHRI laboratory confirmed the identifications of all submitted isolates from 4 hospitals. Among the 574 isolates, 52 (9.1%) were identified differently by the hospitals and by the NHRI laboratory. Hospitals using the germ tube test as the first step in yeast identification had fewer inconsistent identifications of isolates than those using other methods (7.4%; 33/448 vs 15.1%; 19/126, $p<0.01$).

The association between the frequencies of inconsistent identifications and the type and location of hospitals is shown in Table 4. Inconsistent identifications were found in 15.5% and 5.8% ($p<0.005$) of isolates from hospitals in the southern and northern Taiwan, respectively. The frequencies of identification inconsistency in medical centers in the southern and northern regions were similar. In contrast, the frequencies of inconsistency in regional and local teaching hospitals between the southern and the northern regions were significantly different (6.8% vs 28.3%, $p<0.001$). The differences in the frequency of inconsistency between non-medical centers in southern and middle (28.3% vs 12%, $p<0.05$) and southern and eastern (28.3% vs 3.9%, $p<0.05$) regions of Taiwan were significant. Medical centers had fewer isolates with inconsistent identifications than regional plus local teaching hospitals (5.5% vs 11.2%, $p<0.05$). Hospitals that use 3 or more methods had fewer isolates with inconsistent identifications than those using less than 3 methods (6.4% vs 11.3%).

Eleven isolates of *C. krusei*, 9 *C. tropicalis*, 6 *Candida guilliermondii*, 5 *C. albicans*, and 5 *C. glabrata* identified by the hospitals were identified as other species by the NHRI laboratory (Table 5). Among the collected isolates, only 1 isolate of *C. dubliniensis* was identified as *C. tropicalis* by one of the contributing hospitals.

Discussion

Results of this study showed that the accuracy of yeast identification in Taiwan depends on 3 factors. First, the performance was better when medical technologists are experienced in yeast identification. Second, participating hospitals using the germ tube test as the first step in identification had higher rates of consistency of identification with the NHRI laboratory. Third, the finding that each method alone resulted in some misidentifications indicates that the use of a combination of 2 methods should be required in every laboratory.

Among the first 50 germ tube tests performed at the NHRI laboratory, 5 isolates of *C. tropicalis* were misidentified as being positive, which is consistent with a previous report that *C. tropicalis* would give a false-positive result in the germ tube test [15]. The long buds of *C. tropicalis* can be misinterpreted as germ tubes of *C. albicans*. Furthermore, *C. tropicalis* will form germ tube-like structures after longer incubation [9,16]. Thus, to avoid the false-positive results, the germ tube test should not be performed for longer than 3 h. In the next 150 tests, only 1 isolate of *C. tropicalis* was mis-

Table 4. Frequency of inconsistency by the type and the location of hospitals

	No. of isolates with inconsistent identifications / No. of total isolates submitted (%)				
	Northern	Central	Southern	Eastern	Total
MC	4/100 (4)	1/29 (3.4)	7/89 (7.9)	–	12/218 (5.5)
RH + LT	12/177 (6.8)	12/100 (12)	15/53 (28.3)	1/26 (3.9)	40/356 (11.2)
Total	16/277 (5.8)	13/129 (10.1)	22/142 (15.5)	1/26 (3.9)	52/574 (9.1)

Abbreviations: LT = local teaching hospital; MC = medical center; RH = regional hospital

identified as being positive in the germ tube test. There was no further false positive germ tube result for the remaining 460 tests. These results demonstrated that experience and aptitude may reduce inconsistencies in the identification of *Candida* species.

Three different hospitals using the same set of methods (germ tube test as the first step followed by the Mycotube method) had different rates of inconsistency. The NHRI laboratory confirmed identifications of all isolates from 1 hospital. However, 6% and 35% of isolates from the other 2 hospitals were identified differently by the hospitals and the NHRI laboratory. Medical centers had fewer isolates with inconsistent identifications than non-medical centers (5.5% vs 11.2%). According to data from the Directorate-General of Budget, Accounting, and Statistics of the Executive Yuan, the northern, central, southern, and eastern regions of Taiwan have approximately 43%, 25%, 29%, and 3% of the total population of Taiwan, respectively [17]. Hospitals in the northern region serve the largest population in Taiwan, and had fewer isolates with inconsistent identifications than the southern region (5.8% vs 15.5%). These findings suggest that experience and aptitude, which were not directly assessed in this study, may account for the accuracy in identification.

Nine of 11 isolates identified by the hospitals as *C. krusei* were identified as *C. albicans* by the NHRI laboratory. These 9 isolates were from 3 hospitals using either the cornmeal agar window method or the germ

Table 5. Inconsistent identifications of isolates

No. of isolates	Hospital Id[a]	NHRI Id[b]	Methods[c]
9	*Candida krusei*	*C. albicans*	A, E or C, E
2	*C. krusei*	*C. parapsilosis*	A, E or A, D, B, C
4	*C. tropicalis*	*C. albicans*	A, B, or A, D, B, C, or C, E
2	*C. tropicalis*	*C. krusei*	A, D, F or C, B
1	*C. tropicalis*	*C. dubliniensis*	A, D, F
1	*C. tropicalis*	*C. parapsilosis*	C, E
1	*C. tropicalis*	*Cryptococcus laurentii*	C, E
3	*C. guilliermondii*	*C. parapsilosis*	A, C, B or C, B
1	*C. guilliermondii*	*C. albicans*	A, B
1	*C. guilliermondii*	*C. glabrata*	G
1	*C. guilliermondii*	*C. tropicalis*	A, B
2	*C. albicans*	*C. glabrata*	A, D, C or C, B
2	*C. albicans*	*C. tropicalis*	A, D, B, C or C, B
1	*C. albicans*	*Saccharomyces cerevisiae*	A, E
2	*C. glabrata*	*C. tropicalis*	A, B or C, B
1	*C. glabrata*	*C. albicans*	A, E
1	*C. glabrata*	*C. guilliermondii*	C, E
1	*C. glabrata*	*C. krusei*	C, B
1	*C. colliculosa*	*C. glabrata*	A, B
1	*C. curvate*	*C. tropicalis*	A, B
1	*C. famata*	*C. guilliermondii*	A, C, B
1	*C. famata*	*C. tropicalis*	A, F
1	*C. intermedia*	*C. lusitaniae*	A, B
1	*C. kefyr*	*C. tropicalis*	C, E
1	*Cryptococcus laurentii*	*C. glabrata*	A, C, B
1	*C. lusitaniae*	*C. guilliermondii*	A, D, C
1	*C. lusitaniae*	*C. guilliermondii*	A, D, H
1	*C. parapsilosis*	*C. albicans*	A, E
1	*C. parapsilosis*	*C. guilliermondii*	A, C, D, G, B
1	*C. sake*	*C. parapsilosis*	B, D, C
1	*C. sake*	*C. krusei*	A, D, B, C
1	*Geotrichum* spp.	*C. tropicalis*	A, E
1	*Zygosaccharomyces* spp.	*C. famata*	A, B
1	*Trichosporon cutaneum*	*Trichosporon beigelii*	C, B

[a]Organism reported by hospitals.

[b]Organism identified by the NHRI laboratory.

[c]Methods used by hospitals: A = germ tube test; B = API-ID32C; C = cornmeal agar window test; D = assimilation method; E = Mycotube; F = API-ID20C; G =VITEK-YBC; H = CHROMagar test.

tube test as the first step in identification followed by the Mycotube (Table 5). The rate of correct identification by the Mycotube method was consistently lower than API-20C among different studies (76.7% vs 90.8%, 68% vs 86.5%) [18,19].

With few exceptions, *C. albicans* and *C. krusei* are similar in morphology. *C. albicans* but not *C. krusei* forms germ tubes in the presence of serum. *C. albicans* forms round blastoconidia and *C. krusei* forms elongated blastoconidia. *C. krusei* usually forms fairly dry colonies, which are distinct from those of *C. albicans*. Some *C. albicans*, however, also form dry colonies. In the Mycotube method, *C. albicans* produces acid in the sucrose panel and *C. krusei* is negative in the same reaction, which is the only difference between *C. albicans* and *C. krusei* among the 10 tests in the Mycotube method according to the manufacturer's instructions. Accurate distinction between these 2 species is important because it may affect the clinical success of fluconazole therapy [5].

The germ tube test should be considered as presumptive even when performed by well-trained staff, because not all *C. albicans* clinical isolates will form germ tube in the presence of serum [9,15]. In this study, 12 (5%) of 242 *C. albicans* isolates did not form germ tubes in the presence of serum. One isolate failed to form germ tubes even after it was re-subcultured, whereas both VITEK-YBC and API-32C methods identified this isolate as *C. albicans*. These results may explain why hospitals using germ tube test as the first step in yeast identification misidentified *C. albicans* as *C. krusei*, especially when *C. albicans* also formed dry colonies. Another possibility is that there were only few cells forming germ tubes in the presence of serum, which have led to a false negative result.

Although the number of yeast infections caused by non-*albicans* species has increased significantly in the past decade [1,20], *C. albicans* was still the most common isolate submitted by the hospitals in this study. Thus, the germ tube test should be the first step for identifying clinically important yeast in microbiological laboratories in Taiwan, which is also suggested in reports from other populations [9,11]. In this study, the sensitivity and specificity of the germ tube test were 95% (230/242) and 98.6% (411/417), respectively. The API, cornmeal agar window test, assimilation method, VITEK-YBC, and other conventional methods can be used as the second step for identification of yeast that do not form germ tubes. The sensitivity of VITEK-YBC and API-32C were 92.6% (412/445) and 98.3% (59/60), respectively. Both API and VITEK are commercially available, but they are not cost-effective [9,11,21]. A machine is required to read the results of the VITEK-YBC, whereas the results of API can be read manually. This may explain why 13 hospitals used the API system and only 2 used VITEK-YBC in this study. In contrast, the cornmeal agar window test, the assimilation method, and other conventional methods are cost-effective. These methods, however, require either more bench time or more experience [21].

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