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Misidentification of Clinical Yeast Isolates by Using the Updated Vitek Yeast Biochemical Card

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The Vitek Yeast Biochemical Card (YBC) is widely used as a rapid identification (RI) (within 48 h) system for clinical yeast isolates. We compared the RI results obtained by the YBC technique with matched results obtained with the API 20C system. The RI of germ tube-negative yeasts isolated from 222 clinical specimens was performed with the YBC system, and the results were compared with those of standard identifications obtained by using the API 20C system and morphology, with additional biochemical reactions performed as required. Commonly isolated yeasts (*Candida albicans* [*n* = 29], *Candida tropicalis* [*n* = 40], *Torulopsis* [*Candida*] *glabrata* [*n* = 28], *Candida parapsilosis* [*n* = 12], and *Cryptococcus neoformans* [*n* = 14]) were generally well identified (115 of 123 [93%] identified correctly, with only *C. albicans*, *C. tropicalis*, and *C. neoformans* mis- or unidentified more than once). The RI of less commonly isolated yeasts included in the YBC database, however, was less successful (54 of 99 [55%] correct). The YBC card failed to identify 42% (10 of 24) of *Candida krusei* isolates, 80% (4 of 5) of *Candida lambica* isolates, 88% (7 of 8) of *Trichosporon beigelii* isolates, and 83% (10 of 12) of *Cryptococcus* isolates (non-*C. neoformans* species). For most identification failures (79%; 42 of 53) there was no identification by the end of 48 h; the other identification failures (21%; 11 of 53) gave definite but incorrect identifications. Of eight rare clinical yeast isolates not included in the Vitek database, six were, correctly, not identified, while two (25%) were falsely assigned a definite RI (one *Hansenula fabianii* isolate was identified as *Rhodotorula glutinis*, and one *Hansenula* isolate [non-*Hansenula anomala*] was identified as *Hansenula anomala*). While the Vitek YBC rapidly and adequately identifies common clinical yeast isolates, it fails in the RI of more unusual organisms.

The incidence of invasive yeast infections has risen along with advances in the care of critically ill patients (4, 12, 13). The correct identification of clinical yeast isolates is essential so that caretakers can make appropriate decisions regarding both the significance of a particular isolate as well as antifungal therapy. However, the correct identification of yeast isolates (other than germ tube-positive *Candida albicans*) has provided a challenge to the clinical mycology laboratory. Requiring from 24 to 72 h for growth and not as metabolically active as bacteria, medically important yeasts at times have forced mycologists to perform lengthy identification protocols, which include biochemical reactions, assimilation and fermentation tests, and morphology evaluations.

The advent of panels that allowed for the rapid identification (RI) of yeasts by accelerating the biochemical reactions (with smaller reaction volumes) and by indexing the results to predetermined databases was welcomed by mycologists (3, 11). Nevertheless, additional assimilation and fermentation reactions and morphologic determinations have occasionally been necessary for definitive yeast identifications, and unease persists regarding the accuracy of the results obtained (10, 14, 15). One recently marketed fully automated system for the identification of yeasts, which uses the biochemical reactions that occur in the inoculated microwells of a plastic card, is the Yeast Biochemical Card (YBC) system (bioMerieux Vitek, Inc., Hazelwood, Mo.). The database for this system has recently been expanded, presumably allowing for the more accurate identification of isolates (5, 6). We performed a study comparing the yeast identifications provided by this automated system with the identifications obtained with a more standardized rapid identification panel (API 20C [bioMerieux Vitek, Inc.], with additional morphology determination and fermentation reactions performed).

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MATERIALS AND METHODS

Organisms. A total of 222 clinical yeast specimens, with the yeasts in these specimens comprising 10 genera and 25 species, were examined in the study. All isolates were obtained from patient specimens submitted to Brooke Army Medical Center. The patients were hospitalized at Brooke Army Medical Center (204 isolates), Wilford Hall Medical Center (4 isolates), the San Antonio State Chest Hospital (10 isolates), or the Veterans Affairs hospital system (4 isolates; M. Rinaldi, Veterans Affairs Mycology Reference Laboratory, San Antonio, Tex.). Typical *C. albicans* isolates, identified by a positive germ tube test in fetal calf serum at 2.5 h (17), were not evaluated in the study, because the application of the YBC technology to this species, which is so easily and rapidly identified, does not seem to be worth the time or the expense involved. Common clinical yeasts (*Candida tropicalis*, *Torulopsis* [*Candida*] *glabrata*, *Candida parapsilosis*, germ tube-negative *C. albicans*, and *Cryptococcus neoformans*) made up 123 of the isolates (see Table 1); the other 99 isolates were relatively uncommon organisms (see Table 2). Although *Geotrichum candidum* is not technically a yeast (17), it is a yeast-like organism, and the data for two *G. candidum* isolates are recorded here because both the API 20C and YBC systems include the organism in their databases. All isolates were maintained on Sabouraud dextrose agar slants at 25°C or were frozen in a cryopreservative solution (PROTECT; Pro-Lab Incorporated, Round Rock, Tex.) at −70°C. Before testing,

isolates kept at room temperature were subcultured at least once on Sabauroud dextrose agar plates, and frozen isolates were subcultured once into Sabauroud dextrose broth and then once onto Sabauroud dextrose agar plates. For the present study, the identification given by the API 20C system was considered correct; discrepancies between the two systems were further evaluated by repeat testing in each system, repeated morphologic evaluations, and the performance of conventional assimilation and fermentation reactions (9, 17). Quality control organisms, recommended by the manufacturers, included *C. albicans* ATCC 14053, *Cryptococcus albidus* ATCC 34140, *Cryptococcus laurentii* ATCC 76483, *C. neoformans* ATCC 76484, and *Torulopsis* (*Candida*) *glabrata* ATCC 2001 for the YBC system and *C. laurentii* ATCC 18803 and *Blastoschizomyces capitatus* ATCC 10663 for the API 20C system. All quality control organisms were correctly identified by the multiple lots of test systems used in the study.

API 20C yeast identification system. All isolates were tested in the API 20C yeast identification system according to the manufacturer's directions. Test strips contain dehydrated reagents sufficient for 19 biochemical tests and a control well. Isolates were picked in sterile fashion off of 48- to 72-h-old Sabouraud dextrose growth plates and were added to the provided agar base medium to constitute a Wickerham 1+ suspension. Suspensions were used to fill the cupules on the test strips as directed by the manufacturer. Fermentation reactions for sucrose, glucose, and cellobiose were performed in parallel for each isolate. Following incubation at 30°C, the growth in each well was recorded at 24, 48, and 72 h. Final identifications were then made when the selection indicated by the Analytical Profile Index was described as excellent, very good, or acceptable. A designation of low selectivity was accepted only if the identification was confirmed by supplemental tests, as recommended by the manufacturer. Multiple lot numbers of the test strips were used over the duration of the study.

YBC. The YBC is a 30-microwell plastic card which is designed for use in conjunction with an automated system (bioMerieux Vitek, Inc.). This system, initially designed for the rapid identification of bacteria (1), consists of a programmed computer, a reader incubator unit, a filling module, a sealing module, and a printer. The system as applied to rapid yeast identification, including the performance of a recently updated database, has been described in detail (5, 14).

All YBC procedures were conducted as instructed by the manufacturer. Microscopic morphology from growth on cornmeal agar was recorded. A McFarland no. 2 standard suspension (as determined by a colorimeter [bioMerieux Vitek, Inc.]) was made by inoculating an 18- to 48-h-old culture into 1.8 ml of a 0.5% NaCl solution. Suspensions were then inoculated into the cards with the filling module, sealed with the sealing module, and then incubated at 30°C for 24 h. The cards were read by the reader module, which required approximately 1 h, the biochemical patterns were analyzed, and the results were printed. For the present study, the identification was considered acceptable if the probability of the first choice presented was greater than or equal to 85%. If an isolate was identified at "≥85% probability" at 24 or 48 h and no further investigation was indicated by the data prompt, the identification was recorded and was considered complete. An answer was not accepted at 24 h, even if "≥85% probability" was indicated, if additional (48 h) incubation time was suggested on the data prompt, or if additional investigations independent of the card were indicated. A 48-h incubation was performed only when indicated. A reading of "no identification" for a yeast isolate which was not in the Vitek expanded database was considered correct.

An isolate was considered misidentified if the correct identification, without qualifications, was not given by the YBC within 48 h. A reading of "no identification" was given if a complete identification was not given within 48 h. A reading of "incorrect identification" was given if a complete identification which did not match the API 20C result was given within 48 h. Over the duration of the study multiple lot numbers of YBC cards were used.

TABLE 1. RI results for common yeasts by Vitek YBC system

Species identification	No. tested	No. correctly identified (% correct)	No. misidentified	
			No identification	Incorrect identification
C. albicans	29	27 (93)	0	2
C. parapsilosis	12	11 (92)	1	0
C. tropicalis	40	38 (95)	0	2
T. (Candida) glabrata	28	27 (96)	1	0
C. neoformans	14	12 (86)	2	0
Total	123	115 (93)	4	4

RESULTS

A total of 222 clinical yeast isolates were tested in parallel by the API 20C and YBC systems. These included 123 common clinical isolates, including 14 *C. neoformans* isolates (Table 1), and 99 uncommon clinical isolates (Table 2). The YBC system correctly identified 169 of 222 isolates (76%). Of the 123 commonly isolated yeasts (*C. albicans*, *C. tropicalis*, *Torulopsis* [*Candida*] *glabrata*, *C. parapsilosis*, and *C. neoformans*) 115 (93%) were correctly identified. Fifty-four of 99 (55%) less commonly isolated yeast strains were correctly identified.

TABLE 2. RI results for uncommon yeasts by Vitek YBC system

Species identification	No. tested	No. correctly identified (% correct)	No. misidentified	
			No identification	Incorrect identification
Blastoschizomyces capitatus	2	0	2	0
Candida guilliermondii	4	4 (100)	0	0
Candida humicola	4	3 (75)	1	0
Candida krusei	24	14 (58)	9	1
Candida lambica	5	1 (20)	4	0
Candida lipolytica	3	1	2	0
Candida lusitaniae	9	8 (89)	0	1
Candida rugosa	5	3 (60)	2	0
Candida stellatoidea	2	1[a]	0	1
Candida zeylanoides	1	1	0	0
Cryptococcus albidus	4	1 (25)	2	1
Cryptococcus laurentii	3	0	2	1
Cryptococcus terreus	1	0	1	0
Cryptococcus uniguttulatus	4	1 (25)	2	1
Geotrichum candidum	2	0	2	0
Hansenula anomala	3	2	1	0
Rhodotorula rubra	7	7 (100)	0	0
Saccharomyces cerevisiae	6	6 (100)	0	0
Sporobolomyces salmonicolor	2	0	1	1
Trichosporon beigelii	8	1 (13)	7	0
Total	99	54 (55)	38	7

[a] Correctly identified as sucrose-negative *C. albicans*.

TABLE 3. Incorrect RI results by Vitek YBC system

Correct identification	Incorrect identification (time to identification)
Candida albicans	*Candida parapsilosis* (24 h)
Candida albicans	*Pichia ohmeri* (48 h)
Candida krusei	*Blastoschizomyces capitatus* (48 h)
Candida lusitaniae	*C. parapsilosis* (24 h)
Candida stellatoidea	*C. albicans*[a] (48 h)
Candida tropicalis	*C. parapsilosis* (24 h)
Candida tropicalis	*C. parapsilosis* (24 h)
Cryptococcus albidus	*Trichosporon pullulans* (48 h)
Cryptococcus laurentii	*Rhodotorula pilimanae* (48 h)
Cryptococcus uniguttulatus	*Cryptococcus neoformans* (48 h)
Sporobolomyces salmonicolor	*Rhodotorula rubra* (48 h)
Hansenula sp., non-*H. anomala*[b]	*Hansenula anomala* (24 h)
Hansenula fabianii[b]	*Rhodotorula glutinis* (48 h)

[a] Incorrectly identified as sucrose-positive *C. albicans*.
[b] Not in YBC database.

Eighty-three percent of the correct identifications were completed in 24 h (93% of correct identifications for common isolates and 63% of correct identifications for uncommon isolates).

Of the 53 misidentifications by the YBC, 42 (79%) were failures to completely identify an isolate within the YBC database, without the requirement for additional studies, within 48 h. The remainder (11 of 53; 21%) were definite but incorrect identifications and are listed in Table 3. Only *C. albicans* and *C. tropicalis* were assigned incorrect identifications more than once; the two isolates of *C. albicans* were incorrectly identified as *C. parapsilosis* and *Pichia ohmeri*, and both incorrect identifications of *C. tropicalis* were of *C. parapsilosis*.

Conversely, no definite species identification was incorrectly assigned by the YBC more than once (Table 3) other than *C. parapsilosis*, which appeared four times. This misidentification was given to one *C. albicans* isolate, two *C. tropicalis* isolates, and one *Candida lusitaniae* isolate. When these four errors are included, the false-positive rate for a final, definite identification of *C. parapsilosis* was 27% (4 of 15).

Of the 42 yeast isolates given no definite identification by the end of 48 h, 32 (76%) prompted a "no identification" designation from the YBC without qualifications or directions for further testing. These 20 isolates included all 7 *Trichosporon beigelii* misidentifications, all 9 of the *Cryptococcus* isolates that were not definitely identified, and 4 of the 9 unidentified *Candida krusei* isolates. Ten (24%) of the 42 isolates received no definite identification at 48 h but were given tentative identifications, with directions for further testing; these included the other 5 isolates of *C. krusei* and both isolates of *B. capitatus*, each of which was correctly identified after additional glucose fermentation reactions were performed. Several days of additional biochemical tests were required before definite identifications could be made for each of the other three organisms (one *C. parapsilosis* isolate and two *Candida lambica* isolates).

Overall, the most frequently misidentified yeasts included *C. krusei* (10 of 24 [42%] isolates misidentified), *T. beigelii* (7 of 8 [87%] isolates misidentified), *Cryptococcus* spp. (non-*C. neoformans*; 10 of 12 [83%] isolates misidentified), *C. lambica* (4 of 5 [80%] isolates misidentified), and *Candida rugosa* (3 of 5 [60%] isolates misidentified). All but one of the *C. krusei* misidentifications were the result of the inability of the YBC to differentiate between the slower-growing and more biochemically inert organisms *C. krusei*, *B. capitatus*, and *Prototheca zopfi* (in particular, the *N*-acetyl-D-glucosamine test remained negative at 48 h). *T. beigelii* and non-*C. neoformans Cryptococcus* misidentifications, similarly, were the result of the slow growth characteristics of these species, which resulted in multiple false-negative biochemical reactions by the end of 48 h of incubation.

In addition to the 222 isolates that had codes in the YBC database, a total of eight unusual isolates not recognized in the database were tested with the YBC system to determine if incorrect assignments of positive identifications would be made (one isolate each of *Rhodotorula minuta*, *Candida aquatica*, *Candida congoblata*, *Candida intermedia*, *Candida magnoliae*, a *Phaeococcus* species, *Hansenula fabianii*, and a *Hansenula* species, non-*Hansenula anomala* [on the basis of the absence of spontaneous ascospore formation (9)]). These isolates were identified with the API 20C system as described above except for the *Phaeococcus* isolate, which was identified morphologically from growth on potato flake agar. The *H. fabianii* isolate was incorrectly identified as *Rhodotorula glutinis* on the basis of differential erythritol, galactose, and raffinose assimilation results (Table 3). The *Hansenula* isolate (non-*H. anomala*) was incorrectly identified as *H. anomala* on the basis of identical assimilation reactions in the absence of data on ascospore formation. The rest of these isolates were, correctly, not identified. In summary, two of eight (25%) clinical isolates not included within the Vitek database were incorrectly assigned definite identifications by the YBC system.

DISCUSSION

The recent emergence of deep fungal infections as a significant problem in immunocompromised hosts has prompted a sense of urgency in the clinical mycology laboratory. Clinical yeast specimens must be rapidly and accurately identified so that appropriate clinical decisions can be made or epidemiologic investigations can be performed (13). In the study described here the Vitek yeast biochemical system correctly identified the common yeasts *C. tropicalis*, *C. parapsilosis*, *T. (Candida) glabrata*, germ tube-negative *C. albicans*, and *C. neoformans*, usually within 24 h (93% of correct identifications). The ability of the YBC system to rapidly identify these common isolates, using an automated system already in place in many clinical laboratories, would seem to be a significant contribution to effective laboratory support.

However, half (99 isolates) of the isolates in the study belonged to genera or species other than those mentioned above. We believe that the YBC performed less than adequately when used for their identification. The particular inability to correctly identify *C. krusei* or *T. beigelii* within the allotted 48 h was notable. The correct and rapid identification of these isolates is particularly important because of their rising incidence in nosocomial settings and the occurrence of relative resistance to antifungal drugs (2, 7, 8, 16, 18). In addition, despite a high percentage of correct RI of *C. neoformans* isolates (12 of 14 [86%]), we suggest that even a false-negative rate of 14% when the 48-h Vitek result alone is considered is too high when considering the ramifications of the delayed identification of this particular organism.

No pattern of assignment of incorrect identifications to a given yeast was apparent, because no yeast species other than *C. albicans* and *C. tropicalis* (two isolates each) was given an incorrect identification more than once. However, the identification of *C. parapsilosis* commonly appeared as an incorrect identification for other species (27% of *C. parapsilosis* identifications). This pattern, which was based on multiple incorrect or delayed biochemical reactions, suggests that independent

confirmation by alternative techniques may be required following a YBC identification of *C. parapsilosis*. Alternatively, Fenn et al. (6) have remarked that the occasional isolate of *C. tropicalis* will be misidentified as *C. parapsilosis* at 24 h with the YBC system and noted that an additional 24 h of incubation may reveal the correct RI.

It is important to evaluate the accuracy of the 48-h YBC RI result because it is the ease with which these data are obtained that has made the system so attractive to general microbiology laboratories that do not possess particular mycologic expertise. In accordance with the results of earlier studies, the YBC had little difficulty with the RI of common yeast isolates (5, 6). Unlike the results presented by El-Zaatari et al. (5), however, our data suggest that the updated YBC system is inadequate for the reliable RI of less common yeasts. If we had, as in the earlier study (5), included the results of further testing beyond 48 h (as directed by the YBC data prompt), another 10 of the 42 unidentified isolates in our study would have been definitively identified, increasing the correct identification rate for uncommon isolates to only 65% (64 of 99). Differences between these studies could be attributable to interlaboratory variability (in equipment, reagents, or especially personnel; only one of us [M.L.B.] performed all tests) or, in part, to the large differences in the ability to rapidly identify two yeasts in particular (i.e., *T. beigelii* and *C. krusei*).

Our data are similar to those presented by Fenn et al. (6), including the particular difficulty that the YBC system has with the RI of *C. krusei*, *T. beigelii*, and *Cryptococcus* species (non-*C. neoformans*). Although the latter investigators also factored supplemental biochemical or morphologic testing into the YBC identifications, they still achieved a correct RI for fewer than 85% of their isolates in these categories. Unlike the difficulties that those investigators experienced with the correct RI of *C. tropicalis*, 95% of the *C. tropicalis* isolates in our study were correctly identified. We also observed the tentative RI of *C. parapsilosis* for *C. tropicalis* at 24 h, like Fenn et al. (6) did, but growth was delayed enough in each case (except for two isolates; see comments above on *C. parapsilosis*) to prompt the direction of an additional 24 h of incubation, at which time the correct RI was given.

When we tested eight rare yeast isolates that were not included in the Vitek YBC database, six were correctly given no identification, but two (25%) were incorrectly assigned an RI of yeasts within the database. One isolate, a *Hansenula* species (non-*H. anomala*), had a biochemical profile identical to that of *H. anomala* but did not spontaneously produce ascospores after lengthy incubation (9). Thus, the YBC system, by the manufacturer's directions using only basic morphologic examinations and rapid biochemical testing, will be inadequate for the classification of rarer isolates if their differentiation is based on more sophisticated morphologic determinations. The other incorrect assignment of an identification for an isolate not within the Vitek database, an *H. fabianii* isolate identified as *R. glutinis*, occurred because of subtle differences between positive reaction rates across multiple biochemical tests. If 25% of rare yeasts are incorrectly assigned an identification of a yeast within the Vitek database, recognition of their pathogenic potential may never occur.

There are at least two reasons for the suboptimal performance of the RI system when applied to unusual organisms. Despite the recent upgrade, the database for the interpretation of the biochemical reactions may still be inadequate (6). In addition, the slower growth characteristics and less active metabolic and biochemical activities of yeasts compared with those of bacteria inherently hamper the technique. For the latter reason, while continued expansion of the database for better differentiation of less common yeasts will be necessary, the use of basic morphologic determinations and biochemical testing for rapid identifications (within 48 h) may prove insurmountably difficult for some yeasts.

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