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Collaborative Evaluation of Antigen Detection by a Commercial Latex Agglutination Test and Enzyme Immunoassay in the Diagnosis of Invasive Candidiasis

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The Cand-Tec *Candida* detection system and enzyme immunoassay for serum mannan were retrospectively compared in a controlled collaborative evaluation of antigen detection in 32 patients with candidiasis proven by biopsy or culture from a normally sterile site and with sera drawn within 7 days of inclusion. With a threshold titer of 1/8, which excluded false-positive results in 17 hospitalized patients without candidiasis, sensitivities for all 32 patients with candidiasis were 44% for the Cand-Tec assay and 17% for the enzyme immunoassay. Both assays provided greater sensitivity when sera were drawn within 24 h of inclusion in the study and in the category of patients with invasive candidiasis (57% by Cand-Tec and 33% by enzyme immunoassay). The Cand-Tec assay gave false-positive results (titer, ≥1/8) in 4 of 6 patients with transient candidemia, in 1 of 20 otherwise healthy patients with rheumatoid factor, and in 1 patient with a positive cryptococcal latex agglutination test. Three serum specimens from 3 of 32 patients with candidiasis contained rheumatoid factor and gave titers of ≥1/8 by the Cand-Tec assay. Detection of serum mannan by enzyme immunoassay was less sensitive but more specific than the Cand-Tec *Candida* detection system for the diagnosis of invasive candidiasis.

Invasive candidiasis is a frequent opportunistic infection, especially in cancer patients with neutropenia (8). Unfortunately, diagnosis by conventional microbiological techniques is difficult. Blood cultures detect candidemia in only 35 to 44% of patients with disseminated candidiasis (17, 21). Fungal surveillance cultures may help predict invasive candidiasis caused by *Candida tropicalis*, but their value for other *Candida* species, including *C. albicans*, remains uncertain (26). Several methods have been evaluated for detecting antibodies to *Candida* species (5, 7). Unfortunately, the inability of profoundly immunosuppressed patients to produce an antibody response combined with an inadequate period for antibody to reach detectable levels results in antibody tests with poor sensitivity and unsatisfactory predictive value for invasive candidiasis (5, 7). A different approach to early diagnosis of invasive candidiasis in immunocompromised patients involves the detection of circulating antigens of the *Candida* species (2, 5, 7, 14). Methods have been devised for detecting the cell wall polysaccharide antigen mannan in serum by monoclonal (25) or polyclonal (6, 9) enzyme immunoassay (EIA), radioimmunoassay (23, 29), latex agglutination (1, 12, 15), or coagglutination (16); detecting a 48-kilodalton cytoplasmic protein antigen by monoclonal EIA (19, 27, 28) or dot immunoassay (18); and detecting a heat-labile glycoprotein antigen by latex agglutination (1, 3, 10, 11, 15, 22, 24). The latter method is commercially available as the Cand-Tec *Candida* detection system (11, 24), but the assay appears to be insensitive (19 to 71%) (1, 3, 10, 11, 15, 22, 24) with a titer of 1/8, which excludes most false-positive results. This lack of sensitivity is especially frequent on single serum specimens (3, 15). The Cand-Tec test was compared with a latex agglutination method for serum mannan in two studies (1, 15), and the mannan test was found to have greater sensitivity and equivalent specificity for invasive candidiasis. We previously reported a retrospective evaluation of the double-antibody sandwich EIA for serum mannan in cancer patients with or without invasive candidiasis, which demonstrated a sensitivity of 65% and a specificity of 100% (6). In the present study, the Cand-Tec test and EIA for serum mannan were compared in a controlled collaborative evaluation of their predictive value in the diagnosis of invasive candidiasis.

MATERIALS AND METHODS

Selection of patients. Sera were obtained from five groups of patients. Group A included 15 serum samples from 15 patients with positive serologic tests to mycoses other than candidiasis (aspergillosis, 3; blastomycosis, 2; coccidioidomycosis, 2; cryptococcosis, 4; histoplasmosis, 4). These sera were tested at the Quebec Provincial Reference Laboratory by immunodiffusion, complement fixation, or latex agglutination. Group B comprised 20 serum samples from 20 otherwise healthy patients who had rheumatoid factor ranging from 32 to 512 IU (Polyartitre; Fumouze Co., Paris, France). Group C contained 100 serum samples from 100 healthy persons who underwent preemployment evaluation at Saint-Luc Hospital. Group D comprised 31 serum samples from 17 control patients without candidiasis (Table 1). Group E included 32 patients with candidiasis recruited from 10 Quebec hospitals over a 22-month period. Predisposing factors for this group are represented in Table 1. Inclusion criteria included candidiasis documented by histopathology or culture of *Candida* species from a normally sterile site and

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TABLE 1. Clinical findings in patients with proven invasive candidiasis, probable invasive candidiasis, sustained candidemia, and transient candidemia and in control patients without candidiasis

Conditions	No. of patients with:				
	Proven invasive candidiasis	Probable invasive candidiasis	Sustained candidemia	Transient candidemia	No candidiasis
Total	13	4	9	6	17
Underlying disease					
Acute myelogenous leukemia	1	1	0	0	0
Acute lymphocytic leukemia	1	3	0	0	1
Solid tumor	1	0	1	2	2
Organ or bone marrow transplantation	3	0	1	1	2
Severe bacterial infection	5	0	4	5	7
Cardiovascular disease	1	0	0	3	1
Innate or acquired immunodeficiency	1[a]	0	0	0	1[b]
Other	0	0	3[c]	2[d]	3[e]
Avg age (yr) (range)	38 (1–74)	42 (30–53)	44 (22–75)	50 (20–80)	40 (2–74)
Sex (no. male/no. female)	9/4	3/1	4/5	6/0	6/11
Predisposing factors					
Neutropenia lasting more than 1 wk[f]	2	4	0	0	1
Chemotherapy	2	4	0	1	2
Radiotherapy	0	0	0	0	0
Corticosteroid therapy	3	1	1	1	4
Broad-spectrum antibiotic therapy	12	4	8	6	17
Surgery	7	0	3	2	6
Diabetes mellitus	0	0	2	1	1
Alcoholism	1	0	0	0	1
Nonfungal infections[g]	8	2	8	5	17
Candida recovered from:					
Blood	8	4	9	6	0
Intravenous catheter	6	0	8	3	0
Deep organ	13	0	0	0	0
Species recovered					
C. albicans	11	3	7	5	0
C. tropicalis	1	0	0	1	0
C. parapsilosis	1	0	1	0	0
C.paratropicalis	1[h]	1[h]	0	0	0
C. krusei	0	1	1	0	0
Candida maculopapular skin rash	1	0	0	0	0
Antifungal treatment					
Amphotericin B (total dose greater than 50 mg)	10	4	6	0	0
Ketoconazole (more than 3 days)	3	0	2	0	0
Flucytosine	0	1	0	0	0
Outcome					
Survival	6	2	9	2	15
Death	7	2	0	4	2

[a] Myeloperoxidase deficiency.
[b] Acquired immunodeficiency syndrome.
[c] Perforated gastric ulcer, intravenous drug abuse, and abdominal trauma; one patient each.
[d] Abdominal trauma and toxic epidermal necrolysis; one patient each.
[e] Rheumatoid arthritis, chronic renal failure, and intravenous drug abuse; one patient each.
[f] Fewer than 1,000 neutrophils per mm^3.
[g] None of the patients had fungal infections other than candidiasis.
[h] Both isolates were recovered from mixed infections with *C. albicans*.

the availability of sera drawn within 7 days before or after the date of candidemia, histopathologic examination, or culture. The clinical charts of the 32 patients were retrospectively reviewed, and the patients were stratified into the following groups according to the probability of invasive candidiasis. (i) Thirteen patients were classified as having invasive candidiasis. Seven of these patients were diagnosed by histopathology and culture, and in the remaining six patients *Candida* species were cultured from a normally sterile site (liver, thorax, lung biopsy, elbow, and abdominal cavity in two patients). (ii) Patients with probable invasive candidiasis (four patients) had underlying leukemia with

neutropenia and a positive blood culture for a *Candida* species. Disseminated candidiasis is probable in this setting (20). (iii) Patients with sustained candidemia (nine patients) had prolonged candidemia (mean, 8 days; range, 3 to 15 days) despite the removal, in eight patients, of an intravenous catheter colonized by a *Candida* species. (iv) Patients with transient candidemia (six patients) had positive blood cultures for a *Candida* species over a maximum of 48 h and did not receive antifungal treatment. They had either a favorable outcome or absence of invasive candidiasis at autopsy. All sera from 27 of the 32 patients were drawn within 2 months of inclusion. For four other patients, all sera were drawn within 2.5 to 4 months of inclusion, and for a single patient the samples were drawn within 33 months. Because of the variability of interval between serum samplings and inclusion, results are presented for all sera drawn and for sera drawn within 7 days or 24 h of inclusion in the study.

Identification of *Candida* species. *Candida* species were identified by standard procedures (4, 13). Presumptive identification of *C. albicans* was made by a positive germ tube test, and other *Candida* species were identified by the formation of pseudohyphae on cornmeal Tween agar and by use of a commercially available yeast identification kit (API 20C; Analytab Products, Plainview, N.Y.).

Agglutination test. The Cand-Tec *Candida* detection system (Ramco Laboratories Inc., Houston, Tex.) was a gift from Amersham Canada Ltd., Oakville, Ontario. The test was performed according to the specifications of the manufacturer as described by Gentry et al. (11). The test was designated positive if the 1/4 dilution showed agglutination. Since studies indicated that a positive threshold dilution of 1/8 was more predictive of invasive candidiasis (10), results were calculated at both dilutions (1/4 and 1/8). Testing was performed blindly under the supervision of the authors. All sera that gave a positive result were tested for rheumatoid factor (RA Test Reagent Kit, Cooper Biomedical Inc., Malvern, Pa.).

Immunoassay for detection of serum mannan. Coded sera were shipped on dry ice to the Division of Mycotic Diseases, Centers for Disease Control. The double-antibody sandwich EIA was performed as previously described (6), and mannan-protein complexes were dissociated by the boiling EDTA procedure (6). Mannan concentrations greater than 2 ng/ml were considered a positive result, and those less than 2 ng/ml were considered a doubtful result. The test was carried out with reagents directed against *C. albicans* serotype A and limited to patient groups D and E.

RESULTS

Identification of Candida species. Thirty-four *Candida* isolates were obtained from 32 patients with candidiasis (*C. albicans*, 26; *C. tropicalis*, 2; *C. parapsilosis*, 2; *C. paratropicalis*, 2; *C. krusei*, 2). One patient had *C. albicans* isolated from the liver and *C. paratropicalis* isolated from blood, and in another patient *C. albicans* and *C. paratropicalis* were recovered from two blood cultures drawn 1 day apart.

Antigen detection in control patients without candidiasis. Titers of ≥1/4 in the Cand-Tec test were observed in 1 serum specimen (titer, ≥1/8) with a cryptococcal latex agglutination titer of 1/32,760, in 2 serum samples (titers, 1/4 and ≥1/8) with rheumatoid factor of 512 IU, in 1 of 100 serum samples from healthy persons (titer, 1/4), and in 5 of 31 serum samples from 17 hospitalized patients without candidiasis. False-positive results in the Cand-Tec assay were not observed at a dilution of 1/8 in the hospitalized control patients. Serum mannan was not detected in 22 serum samples from 14 hospitalized patients without candidiasis. Specificity, defined as the percentage of hospitalized control patients with negative test results, was 100 and 76% in the Cand-Tec assay at titers of ≥1/8 and 1/4, respectively. The specificity of the EIA for serum mannan was 100% in this control patient population.

TABLE 2. Results of Cand-Tec agglutination and EIA for serum mannan in patients with candidiasis

Category	No. of patients with the following results:							
	Cand-Tec				EIA			
	≤1/2	1/4	≥1/8	Total	0	<2 ng/ml	≥2 ng/ml	Total
Invasive candidiasis	5	2	6	13	10	0	3	13
Probable invasive candidiasis	3	1	0	4	1	0	2	3
Sustained candidemia	3	2	4	9	6	1	1	8
Transient candidemia	1	1	4	6	4	1	0	5

Antigen detection in patients with candidiasis. Table 2 shows the results of antigen detection by Cand-Tec agglutination and EIA for serum mannan in patients with different categories of candidiasis. Antigen was detected by the Cand-Tec assay at a titer of ≥1/8 in 6 of 17 patients and by the EIA in 5 of 16 patients with invasive or probably invasive candidiasis. The Cand-Tec assay detected antigen in four of six patients with transient candidemia, but mannan (≥2 ng/ml) was detected in none of five patients in this category of candidiasis. The sensitivity of the Cand-Tec assay and EIA for serum mannan in patients with candidiasis is shown in Table 3. Both assays provided greater sensitivity when sera were drawn within 24 h of inclusion in the study and in the category of patients with invasive candidiasis (57% by Cand-Tec and 33% by EIA).

Eighteen of 26 patients infected with *C. albicans* had a Cand-Tec titer of ≥1/4 (1/4 titer, 6 patients; ≥1/8 titer, 12 patients). Sera from three of the 18 patients, however, contained rheumatoid factor and were negative in the mannan EIA. Four of 26 patients infected with *C. albicans* had detectable serum mannan (≥2 ng/ml, three patients; <2 ng/ml, one patient).

Antigen was detected by both assays in two patients infected with *C. tropicalis*. The two patients infected with *C. paratropicalis* and the two patients infected with *C. krusei*, however, had negative results by Cand-Tec and EIA.

Three sera from three patients (one with transient candidemia and two with sustained candidemia; Table 2) contained rheumatoid factor and gave titers of 1/8 to 1/32 by the Cand-Tec assay. If these sera were withdrawn from analysis, sensitivities at a titer of 1/8 (Table 3) decreased from 44 to 34% for all patients with candidiasis, from 24 to 21% for all sera, from 34 to 29% for sera drawn within 7 days of inclusion, and from 44 to 36% for sera drawn within 24 h of inclusion in the study.

DISCUSSION

The clinical and microbiological diagnosis of invasive candidiasis is difficult. One approach to early diagnosis involves the detection of circulating antigens of *Candida* species. In candidiasis, methods have been devised for detecting the cell wall polysaccharide antigen mannan in serum by monoclonal (25) or polyclonal (6, 9) EIA, radioim-

TABLE 3. Sensitivity of Cand-Tec agglutination and EIA for serum mannan in patients with candidiasis

Category	Total no. of patients or sera	Cand-Tec								EIA				
		Titer of ≥1/4				Titer of ≥1/8				No. of patients or sera		Sensitivity (%)	PPV (%)	NPV (%)
		n	Sensitivity (%)	PPV[a] (%)	NPV[b] (%)	*n*	Sensitivity (%)	PPV (%)	NPV (%)	Total	Mannan level of ≥2 ng/ml			
All patients and sera														
All patients	32	21	66	74	69	14	44	100	64	29	5	17	100	55
All sera	118	47	40	71	58	28	24	100	57	74	6	8	100	52
Sera, 7 days[c]	62	30	48			21	34			40	6	15		
Sera, 24 h[d]	36	20	55			16	44			21	4	19		
Invasive candidiasis														
Patients	13	8	61	72	66	6	46	100	65	13	3	23	100	56
Sera, 7 days	34	17	50			15	44			19	4	21		
Sera, 24 h	21	13	62			12	57			9	3	33		
Probable invasive candidiasis														
Patients	4	1	25	51	50	0	0	0	50	3	2	66	100	75
Sera, 7 days	4	1	25			0	0			3	2	66		
Sera, 24 h	1	0	0			0	0			1	1	100		
Sustained candidemia														
Patients	9	6	67	74	70	4	44	100	64	8	1	12	100	53
Sera, 7 days	18	8	44			4	22			13	7	54		
Sera, 24 h	13	6	46			3	23			10	4	40		
Transient candidemia														
Patients	6	5	83	78	82	4	66	100	75	5	0	0	0	50
Sera, 7 days	6	4	66			2	33			5	0	0		
Sera, 24 h	1	1	100			1	100			0	0	0		

[a] PPV, Positive predictive value.
[b] NPV, Negative predictive value.
[c] Sera drawn within 7 days of inclusion in the study.
[d] Sera drawn within 24 h of inclusion in the study.

munoassay (23, 29), latex agglutination (1, 12, 15), or coagglutination (16); detecting a 48-kilodalton cytoplasmic protein antigen by monoclonal EIA (19, 27, 28) or dot immunoassay (18); and detecting a heat-labile glycoprotein antigen by commercial Cand-Tec agglutination (1, 3, 10, 11, 15, 22, 24). In two published studies, detection of serum mannan by latex agglutination was found to have greater sensitivity and equivalent specificity for invasive candidiasis when compared with the Cand-Tec assay (1, 15). We previously reported a retrospective evaluation of the double-antibody sandwich EIA for serum mannan in cancer patients with or without invasive candidiasis; the assay demonstrated a sensitivity of 65% and a specificity of 100% (6). In the present controlled, collaborative evaluation, we retrospectively compared the Cand-Tec assay and EIA for serum mannan in sera of patients stratified according to the probability of invasive candidiasis and of control patients without candidiasis. Sera from neutropenic leukemia patients with candidemia, who did not undergo autopsy, were classified as probable invasive candidiasis, because it has been reported that 88% of patients with *C. albicans* and 81% of patients with *C. tropicalis* fungemia occurring in this setting have either disseminated or focal invasive disease due to the fungus (20). Sera from normal blood donors were not assayed for mannan because it was previously shown that the antigen is uniformly undetectable by EIA in this control population (6).

The sensitivity of the EIA for serum mannan in patients with proven invasive candidiasis (23%) was lower than that observed in a previous study (65%) (6) with identical reagents. The mean number of serum samples tested per patient, however, was greater in the previous (7.5) than in the present (3.0) study, and this difference can affect sensitivity data because the presence of antigen in serum is often transient (6, 15). In addition, patients in the present study were not as profoundly immunosuppressed as those in the previous evaluation. The degree of immunosuppression of these populations may influence the production of antibodies to mannan and consequently the clearance of circulating antigen. The proximity of serum collection to the time of diagnosis can also influence diagnostic sensitivity, especially if antigenemia is not sustained but transient. Both the Cand-Tec assay and the EIA for serum mannan produced greater sensitivities in sera drawn within 24 h of inclusion in the study. This observation suggests that optimal diagnostic sensitivity would require at least weekly serum samplings.

The results of this study agree with published clinical evaluations (1, 3, 10, 11, 15, 22, 24) of the Cand-Tec test. These demonstrated that a titer of 1/8 is usually diagnostic of invasive candidiasis, whereas a titer of 1/4 occurs more commonly in invasive disease but is also found in control patients without candidiasis. However, titers of ≥1/8 were observed not only in patients with invasive candidiasis but also in 66% of patients with transient candidemia. The EIA for serum mannan was more specific, and antigen (≥2 ng/ml) was not detected in patients with transient candidemia. The Cand-Tec kit does not contain control latex sensitized with normal rabbit serum, and thus false-positive results due to rheumatoid factor were observed, as in previous reports (3). Since the antigen detected by the Cand-Tec assay has not

been definitely characterized as a component of the fungus, it is not known whether it contains shared epitopes with cryptococcal capsular polysaccharide. The sensitivity of the antigen to heat and the inability of sensitized latex to agglutinate mannan (11) suggest that the circulating Cand-Tec antigen is not mannan.

In previous reports, the Cand-Tec test (1, 3, 11, 15) and EIA for serum mannan (6) detected antigenemia in patients infected with *C. albicans*, *C. parapsilosis*, or *C. tropicalis*. Both methods appeared to be insensitive in patients infected with *C. krusei*, *C. parapsilosis*, or *C. paratropicalis*, but the numbers were too small to draw firm conclusions.

The moderate sensitivities of the Cand-Tec assay and EIA for serum mannan do not provide optimum negative predictive value for invasive candidiasis. The high specificity of the EIA for serum mannan, however, suggests that the presence of this circulating antigen in patients at risk is closely correlated with visceral candidal infection.

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