Candida Detection System (CAND-TEC) to Differentiate between Candida albicans Colonization and Disease

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Received 30 January 1986/Accepted 17 June 1986

Eighty-three serum specimens from 24 patients infected with Candida albicans were examined for circulating Candida protein antigens with the Candida Detection System (CAND-TEC; Ramco Laboratories, Inc., Houston, Tex.). The medical records of each patient were reviewed for clinical evidence of Candida colonization or disease, predisposing factors for infection, underlying illness, the presence of a contaminated indwelling venous catheter, intravenous amphotericin B therapy, and outcome. Forty-nine serum specimens with antigen titers of 1:2 or less were obtained either from colonized patients or at a time when disseminated disease was not yet clinically suspected. Except for five specimens from two colonized patients, one with a contaminated arterial line, the other specimens with titers of 1:8 or greater (n = 14) were obtained from patients who had been clinically diagnosed and treated for disseminated candidiasis. Serum specimens with titers of 1:4 were often from patients with deep-seated candidal infection but were not uniformly diagnostic; in this situation additional specimens should be tested for Candida antigen titers. Only 1 of 24 serum specimens from patients with no evidence of C. albicans infection had a Candida protein antigen titer of 1:8. With a 1:8 or greater titer as a criterion for dissemination, the sensitivity of the CAND-TEC system was 71%, with a specificity of 98%. If the 1:8 titer for the colonized patient with a contaminated arterial line is not considered a false-positive result, the CAND-TEC sensitivity was 83%. The latex agglutination assay appears to be a useful, rapid, and noninvasive means of laboratory diagnosis of systemic candidiasis. The recovery of C. albicans from at least three body sites may also be a useful predictor of disseminated disease.

With increasing therapeutic modalities available for medical care, the incidence of systemic candidiasis has increased. For example, in leukemic patients, Candida infection rates observed at autopsy increased from 2% for the period 1963 to 1970 to 35% for the period 1971 to 1975 (9). Trauma, broad-spectrum and multiple narrow-spectrum antimicrobial coverage, steroid therapy, carbohydrate-rich diets, and indwelling urinary or intravenous (i.v.) catheterization are factors which predispose individuals to candidiasis (12).

The diagnosis of deep-seated Candida infections is difficult. Only 15 to 40% of patients with postmortem evidence of disseminated candidiasis were treated premortem for the disease (3). Presently, diagnosis of disseminated candidiasis is primarily clinical. Definitive confirmation is by histopathologic demonstration of candidal invasion of visceral tissue (4). Laboratory diagnosis of candidiasis has included culture, antibody detection, and antigen detection.

Isolation of Candida albicans from clinical specimens must be interpreted with caution. This is especially true with hospitalized patients who have a higher Candida colonization rate than do healthy individuals. For example, oral and fecal C. albicans prevalence is approximately 10% for normal adults and 20% or higher for hospitalized patients (12). The isolation frequency of C. albicans is 15% for vaginal specimens from healthy women and 10% for urine specimens; it is isolated infrequently from skin samples from normal subjects and at a variable rate from sputum specimens (12). Blood cultures are positive for only 44% of patients with autopsy-proven candidiasis (11). Conversely, candidemia does not always lead to systemic disease (15). Fungal surveillance cultures also are not good predictors of systemic C. albicans infections (13). However, multiple positive cultures do correlate with systemic C. tropicalis infections (13).

Serodiagnostic methods for detecting antibodies to Candida spp. have included counterimmunoelectrophoresis, double diffusion, immunoelectrophoresis, immunofluorescence, radioimmunoassay, and enzyme-linked immunosorbent assay (3, 12). The sensitivity of these assays in diagnosing systemic candidiasis has ranged from 50 to 92% for immunocompetent patients, with an even lower sensitivity of detection for immunosuppressed patients (3, 8). These assays, however, lack specificity in distinguishing between colonization and deep-seated infection (3).

The insensitivity of antibody detection in immunosuppressed patients has led to serodiagnostic tests for circulating Candida antigens. The Candida antigen examined in most of these assays is mannann, the major component of Candida cell walls. Although mannann antigenemia is detected at higher rates in immunosuppressed patients than antibodies are (9), the sensitivity is still only 50 to 70% (3, 9). Increased detection might be obtained if the mannans of both C. albicans serotypes (A and B) were used. Serotype A accounts for 74% of the clinical isolates of C. albicans (1).

Candidal metabolites such as mannose and arabinitol have been detected in serum by gas-liquid chromatography. When the arabinitol-to-creatine ratio in serum was examined, the sensitivity and specificity of diagnosing invasive candidiasis were 64 and 96%, respectively (6).

Recently, a commercially available latex agglutination test for the detection of circulating Candida protein antigens was introduced. This study examined the ability of this test to
TABLE 1. Clinical data for patients infected with C. albicans

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Status of Candida infection</th>
<th>Underlying illness</th>
<th>Predisposing factor</th>
<th>Antifungal therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Candidemia</td>
<td>Acute myelogenous leukemia</td>
<td>AM, IV</td>
<td>IVAMB, 5FC</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Systemic candidiasis</td>
<td>SLE</td>
<td>AM, IV, NT</td>
<td>IVAMB, N</td>
<td>Survival</td>
</tr>
<tr>
<td>3</td>
<td>Colonic abscess</td>
<td>Hairy cell leukemia</td>
<td>AM, IV</td>
<td>IVAMB</td>
<td>Survival</td>
</tr>
<tr>
<td>4</td>
<td>Systemic candidiasis</td>
<td>Chronic obstructive pulmonary disease</td>
<td>AM, IV, FC</td>
<td>IVAMB</td>
<td>Survival</td>
</tr>
<tr>
<td>5</td>
<td>Pericardial candidiasis</td>
<td>Alcoholic hepatitis, diabetes mellitus</td>
<td>AM, IV</td>
<td>IVAMB</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>Systemic candidiasis</td>
<td>SLE</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>7</td>
<td>Bladder colonization</td>
<td>Hodgkin’s lymphoma</td>
<td>AM, IV, FC</td>
<td>AMBIR</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>Candida esophagitis</td>
<td>AIDS, Hodgkin’s lymphoma</td>
<td>AM, IV</td>
<td>N, AMBIR</td>
<td>Survival</td>
</tr>
<tr>
<td>9</td>
<td>Normal flora or colonization</td>
<td>Parkinson’s disease</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>10</td>
<td>Oral thrush</td>
<td>Multiple congenital anomalies</td>
<td>AM, FC, IV</td>
<td>AMBIR, NO</td>
<td>Death</td>
</tr>
<tr>
<td>11</td>
<td>Oral thrush, bladder colonization</td>
<td>Chronic obstructive pulmonary disease</td>
<td>AM, IV</td>
<td>N, AMBIR</td>
<td>Survival</td>
</tr>
<tr>
<td>12</td>
<td>Oral thrush</td>
<td>Lung carcinoma</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>13</td>
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<td>SLE</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>14</td>
<td>Oral thrush</td>
<td>Acute myelomonocytic leukemia</td>
<td>AM, IV</td>
<td>CL, IVAMB</td>
<td>Death</td>
</tr>
<tr>
<td>15</td>
<td>Oral thrush</td>
<td>N</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>16</td>
<td>Oral thrush</td>
<td>Acute myelomonocytic leukemia</td>
<td>AM, IV</td>
<td>IVAMB, N</td>
<td>Survival</td>
</tr>
<tr>
<td>17</td>
<td>Candida esophagitis</td>
<td>Hodgkin’s lymphoma</td>
<td>AM, IV, FC</td>
<td>AMBIR</td>
<td>Death</td>
</tr>
<tr>
<td>18</td>
<td>Bladder colonization</td>
<td>Multiple sclerosis</td>
<td>AM, IV</td>
<td>AMBIR</td>
<td>Survival</td>
</tr>
<tr>
<td>19</td>
<td>Normal flora or colonization</td>
<td>Liver carcinoma</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>20</td>
<td>Bladder colonization</td>
<td>Multiple congenital anomalies</td>
<td>AM, NT, IV</td>
<td>AMBIR, NO</td>
<td>Death</td>
</tr>
<tr>
<td>21</td>
<td>Bladder colonization</td>
<td>Bladder carcinoma</td>
<td>AM, NT, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>22</td>
<td>Bladder colonization</td>
<td>Toxic epidermal necrolysis</td>
<td>AM, FC, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
<tr>
<td>23</td>
<td>Superficial skin wound</td>
<td>Peripheral vascular disease</td>
<td>AM, IV</td>
<td>NIR</td>
<td>Survival</td>
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<tr>
<td>24</td>
<td>Normal flora or colonization</td>
<td>Common bile duct tumor</td>
<td>AM, IV</td>
<td>N</td>
<td>Survival</td>
</tr>
</tbody>
</table>

* SLE, Systemic lupus erythematosus; AIDS, acquired immunodeficiency syndrome.
* AM, Antimicrobial agents; IV, catheter; FC, Foley catheter; NT, nephrostomy tube.
* IVAMB, i.v. amphotericin B; 5FC, 5-fluorocytosine; N, oral nystatin; AMBIR, amphotericin B irrigation; CL, clotrimazole; NO, nystatin ointment; NIR, nystatin irrigation.

distinguish between patients with deep-seated candidiasis and those colonized with C. albicans.

MATERIALS AND METHODS

Serum specimens. Serum specimens from 24 patients with C. albicans isolated from one or more sites and from 24 patients with no fungus isolated from at least 10 specimens were examined for circulating Candida antigens. The serum specimens obtained were those that had been submitted for blood chemistry tests. The serum specimens were stored at 1 to 8°C for not more than 6 days before Candida protein antigen testing.

Isolation and identification of C. albicans. Specimens requested for routine bacteriological or fungal cultures or both were processed as outlined in the Manual of Clinical Microbiology (14). Yeasts were identified as C. albicans either by demonstration of germ tube production at 3 h of incubation in serum at 35°C (14) or by assimilation profiles with the API 20C System (Analytab Products, Plainview, N.Y.).

Candida antigen detection. Circulating Candida protein antigens were detected in serum with the Candida Detection System, CAND-TEC (Ramco Laboratories, Inc., Houston, Tex.). Sera were diluted 1:2 with the diluent supplied in the kit. The diluted specimen (20 µl) was mixed with 20 µl of latex particle coated with rabbit anti-Candida antibody. The mixture was rotated at 140 rpm for 10 min in a moist chamber and then read immediately for agglutination. Specimens with positive screens at 1:2 for Candida antigen were further titrated by using twofold serial dilutions. The endpoint was read as the highest dilution with positive agglutination.

Circulating mannann antigen was detected with the LA-Candida Antigen Detection System (Immuno-Mycologics, Inc., Norman, Okla.). Patient serum (300 µl) was mixed with 50 µl of detacher enzyme and incubated at 56°C for 15 min, and the reaction was stopped by the addition of an enzyme inhibitor. The detacher enzyme is a proteolytic enzyme which destroys antibodies associated in immune complexes, thus liberating mannan antigen for detection. The treated sera were tested undiluted and at a 1:10 dilution by mixing 2 drops of serum with 1 drop of latex particle sensitized with rabbit anti-Candida globulin. After the mixture was rotated at 160 rpm for 5 min in a moist chamber, the agglutination was read immediately. A low Candida mannan antigen control is included in the system kit. The control does not have to be treated with detacher enzyme or enzyme inhibitor before testing with sensitized latex reagent.

Patient groups. Patients were divided into two groups based on whether C. albicans had or had not been isolated. To determine whether the C. albicans isolated was causing disease, patient charts were reviewed for: (i) clinical observations made by the attending physician, (ii) evidence of predisposing factors for Candida infection, such as underlying illness, use of antimicrobial agents, hyperalimentation, and catheterization, (iii) evidence of i.v. catheterization, (iv) evidence of i.v. amphotericin B therapy, (v) outcome, and (vi) in those cases in which postmortem were performed, histopathological results. Clinical impressions were based on microbiological findings, the presence of predisposing factors for Candida colonization and dissemination, patient clinical history, and patient progress with antimicrobial or other therapeutic approaches.

RESULTS

Serum specimens from 24 patients with cultures positive for C. albicans were tested for circulating candidal antigen. A clinical or histopathological diagnosis of systemic or deep-seated candidiasis was made for six patients (patients 1 through 6; Table 1). Patients 5 and 6 were diagnosed as
having disseminated candidiasis at postmortem. Of the 18 colonized patients, 10 (patients 8 through 17) had evidence of oral candidiasis, and 7 of these had a long history of this disease. Urinary tract colonization was present in six patients (patients 7 and 18 through 22). In three patients (patients 9, 19, and 24), *C. albicans* was considered to be either part of the normal flora or a colonizer since no mention was made about *C. albicans* culture results in the charts and the patients were not treated for the organism.

Patient 5 was admitted for alcoholic hepatitis, hallucination, progressive weakness, and loss of consciousness. She was placed on triple antimicrobial coverage for possible sepsis. *C. albicans* grew in several cultures of sputum and urine taken within the first 2 weeks after admission. Although systemic candidiasis was considered, antifungal therapy was withheld since there were no overt signs suggesting dissemination, such as candidal endophthalmitis, cutaneous lesions, or positive blood cultures. During week 3 of hospitalization, a catheter tip yielded *C. albicans*, and *Klebsiella oxytoca* grew in blood cultures. During week 5 the patient became comatose, and amphotericin B therapy was initiated. The patient died a week later. Histopathological evidence at postmortem suggested *Candida* pericarditis.

Patient 6 had a history of systemic lupus erythematosus and a left arm lesion which was skin grafted. The skin had been infected with *Staphylococcus aureus*. On admission, it was noted that she had *Candida esophagitis*. During week 1 of hospitalization, her arm ulcer was debrided, and histopathological examination of the skin biopsy showed yeastylike organisms by hematoxylin and eosin stain but not by periodic acid, Gram, or Gomori methenamine-silver stain. Deep-seated candidiasis was not suspected premortem. Necropsy revealed yeast invasion of the thyroid, liver, and heart tissues. *C. albicans* was cultured from postmortem lung and blood specimens.

The underlying illnesses of the patients are listed in Table 1. In 11 patients, the underlying illness was leukemia, lymphoma, or a solid tumor. In addition to the seven patients with a long-standing history of oral candidiasis, four other patients also had a previous microbiological or clinical history of *Candida* infections. In the remaining 13 patients, *C. albicans* was first isolated between day 2 and week 10 of hospitalization. In all 13 patients, two or three antimicrobial agents were being administered at the time *C. albicans* was isolated.

Amphotericin B was administered i.v. to six patients, four with disseminated candidiasis and two with only *Candida* colonization. In one patient with disseminated candidiasis, 5-fluorocytosine was added to the amphotericin B therapy. The one patient with disseminated candidiasis who was not treated with amphotericin B (patient 3) had abdominal candidal abscesses. The illness resolved after incision and complete drainage of all abscesses. Two patients (patients 14 and 16) considered clinically to be colonized with *C. albicans* were given i.v. amphotericin B. Patient 14 had pharyngeal candidiasis unrelieved by clotrimazole therapy. This patient was also treated with i.v. amphotericin B. In patient 6, i.v. amphotericin B was given after repeated episodes of fever, and therapy was continued for 2 weeks. The patient subsequently had an episode of *S. aureus* bacteremia which led to his death.

Microbiological culture results for specimens obtained from these patients are listed in Table 2. *C. albicans* was recovered from blood cultures of three patients with disseminated candidiasis. The yeast was isolated from six sets of blood cultures during a 1-week period from patient 1, from eight sets during a 2-week period from patient 2, and from only one set from patient 3. No *C. albicans* was isolated from blood cultures of patients 4 and 5 with disseminated disease. The yeast was isolated from one premortem and one postmortem blood culture set from patient 6 with disseminated candidiasis. Two patients (patients 11 and 21) considered to be only colonized with *C. albicans* also had the yeast isolated from their blood cultures. Both patients had an
arterial line contaminated with *C. albicans*. *C. albicans* was isolated from specimens taken from multiple sites in 18 of the 24 patients. Five of the six patients with disseminated disease had *C. albicans* isolated from three or four body sites. Patient 5 with pericardial candidiasis had *C. albicans* isolated premortem from two sites. Four patients (patients 11, 13, 20, and 21) with *C. albicans* colonization had the yeast isolated from three body sites, whereas the 14 other patients with *C. albicans* colonization had the organisms isolated from one or two sites.

The titers of circulating *Candida* antigen for each patient from whom *C. albicans* was isolated are presented in Table 2. Of the 83 serum specimens tested from these 24 patients, 36 exhibited no agglutination with the *Candida* latex reagent. Of the 36 seronegative serum specimens, 34 were obtained from colonized patients. Two serum specimens with no detectable *Candida* antigen were from patients with disseminated disease; one was obtained from patient 1 early during hospitalization, 6 days before any *C. albicans* culture isolation, and one was obtained from patient 4 10 days after i.v. amphotericin B therapy. Thirteen serum specimens had a 1:2 titer of circulating candidal antigen; six were from colonized patients, and seven were from three patients (patients 1, 2, and 5) with deep-seated candidiasis. The single serum sample from patient 1 with a 1:2 titer was obtained 1 day before any *C. albicans* culture isolation. The four serum specimens from patient 2 with 1:2 titers were obtained more than 1 week before clinical suspicions of disseminated disease and i.v. amphotericin B therapy; one serum sample was obtained 1 day after one blood culture set yielded *C. albicans*. Thirteen serum specimens had titers of 1:4; 3 were from colonized patients, and 10 were from patients with disseminated disease. Eleven serum specimens had titers of 1:8; five were from two colonized patients, one with an arterial line contaminated with *C. albicans*, and six were from patients with deep-seated *C. albicans* infection. All 10 serum specimens with titers of 1:16 or higher were from patient 3, who had abdominal abscesses with *C. albicans*, or from patient 6, who had histological evidence of deep-seated infection.

The course of illness for the four patients with deep-seated candidiasis diagnosed premortem is shown in Fig. 1. In patient 1, *Candida* infection may have occurred between days 8 and 9 of hospitalization since *Candida* antigen titers increased during this time from 1:2 to 1:8. *Candida* antigen was positive in this patient before culture results were positive. The status of patient 3 was postcolonic infarction secondary to vasculitis associated with hairy cell leukemia. During two colonic surgeries during his hospital stay, sections of necrotic colon were excised. The wound was closed, but some drainage of sanguinous fluid was noted from the most lateral aspect of the wound which had been left open. Although *C. albicans* grew from blood and abscess drainage, the patient was not treated for *C. albicans* and was discharged. He returned 1 week later with fever, chills, and vomiting. Abdominal abscesses were drained and again *C. albicans* grew from the drainage. The *Candida* protein
antigen titers during his first hospitalization indicated deep-seated infection. The titer remained high on readmission. Unfortunately, subsequent sera were not obtained. Patient 4 had acute renal failure and fever for more than 3 weeks. On the day of initiation of i.v. amphotericin B therapy, the *Candida* protein antigen titer was 1:8. By day 10 of therapy, no *Candida* protein antigens were detectable and kidney function improved. Defervescence occurred on day 1 of therapy, and the patient was afebrile on day 3 of treatment.

Except for patient 11, who had an arterial line contaminated with *C. albicans*, the only colonized patient with *Candida* protein antigen titers greater than 1:4 was patient 7. Two weeks before her death, *C. albicans* grew in multiple urine cultures. Serum specimens taken 2 weeks prior to and at death yielded 1:8 titers of *Candida* protein antigens. There was no clinical suspicion of deep-seated candidiasis, and no *C. albicans* was found at autopsy. Twenty-four serum specimens from 24 patients with no *C. albicans* isolated were tested for circulating candidal protein antigens. Twenty-one serum specimens had no detectable antigens. There was one serum specimen each with a titer of 1:2 or 1:4. One serum specimen had a 1:8 *Candida* antigen titer and was from a patient with psoriasis exacerbated by secondary infection with *S. aureus*.

Eighty-one serum specimens obtained from patients with positive *Candida* cultures were also tested for circulating mannan antigen. They included 13 serum specimens with *Candida* antigen titers of 1:4 and 19 serum specimens with high titers of ≥1:8. Mannan antigen was not detected in any of the 81 sera. However, the low *Candida* mannan antigen control supplied in the LA-Candida Antigen Detection System did agglutinate with the sensitized anti-*Candida* latex reagent.

DISCUSSION

In this study, we examined whether the presence of circulating antigens differentiated between colonization and systemic candidiasis. The correlation was based on clinical evidence of disease. The CAND-TEC latex reagent detects protein antigens of *C. albicans* and of other *Candida* species such as *C. stellatoideae*, *C. tropicalis*, and *C. parapsilosis*. The antigen detected is not mannan, which is a carbohydrate and is heat stable (15). The sera used for detecting circulating *Candida* antigens must not be heat inactivated or treated in any manner which would result in protein denaturation.

According to the manufacturer, a *Candida* antigen titer of 1:4 or greater is consistent with systemic candidiasis. On the other hand, a serum specimen failing to agglutinate with the sensitized latex reagent suggests that no *Candida* infection or disease is present. In our series, all 57 serum specimens with no detectable *Candida* antigen were obtained either from colonized patients or from a patient with no evidence of *C. albicans* infection. The 14 serum specimens with titers of 1:2 were also obtained either from noninfected or colonized patients or at a time when disseminated disease was not yet clinically suspected. Except for sera from three patients, one with a contaminated arterial line, all other sera with titers of 1:8 or greater were obtained from patients clinically diagnosed and treated for disseminated candidiasis. Although 10 serum specimens with *Candida* protein titers of 1:4 were from patients with deep-seated *C. albicans* infection, 4 were not. We suggest that patients with 1:4 titers be retested for *Candida* antigen with additional sera. In the three colonized patients with 1:4 *Candida* antigen titers, subsequent sera had titers of 1:2 or less. The two serum specimens from patient 5 with disseminated disease had titers of 1:2. Both serum specimens were obtained early during the hospitalization of the patient, approximately 1 month before i.v. amphotericin B therapy and death. Perhaps additional specimens obtained from patient 5 closer to the time of death would have yielded higher circulating *Candida* antigen titers.

Six patients had deep-seated candidiasis, 18 were colonized, and 24 had no evidence of *C. albicans* infection. Patients with titers of 1:8 or greater included five patients with disseminated candidiasis, one colonized patient with a contaminated arterial line, and an uninfected patient. Based on these results, the CAND-TEC system showed a sensitivity of 71% in diagnosing deep-seated candidiasis. However, if the 1:8 titer for the colonized patient with a contaminated i.v. catheter is not considered a false-positive result, the CAND-TEC sensitivity was 83%. The specificity of CAND-TEC was 98%. By lowering the titer criterion for *Candida* dissemination to 1:4 or greater, the CAND-TEC sensitivity is decreased to 45 to 50% due to increased numbers of false-positive results; the specificity remains 97%. Our results with the commercially available CAND-TEC reagents were similar to those reported by Gentry et al. (5) for a similar system. In their series, none of the sera from control or colonized *Candida* patients had titers above 1:2. Of the sera obtained from patients with systemic candidiasis, 91% had titers of 1:4 or greater. These investigators also observed a correlation between circulating *Candida* antigen titers and the prognosis of the patient. They reported a decrease in *Candida* antigen titers with effective antifungal therapy. In patient 4, the *Candida* antigen titer decreased from 1:8 to 1:2 with 10 days of i.v. amphotericin B therapy.

It was surprising that none of the sera from patients with deep-seated candidiasis in this series had detectable mannan antigen. A possible explanation may be the relative insensitivity of mannan detection. First, mannan levels rarely exceed 100 ng/ml in sera from heavily infected *Candida* patients (7, 9). Second, the anti-*Candida* serum for latex sensitization was prepared only against *C. albicans* serotype A. We did not determine serotype for our *Candida* isolates. It seems unlikely that all deep-seated *Candida* isolates were serotype B. Third, the mannan test has a 40% sensitivity in determining deep-seated *Candida* infections in immunocompromised hosts (10, 15). Of the 13 serum specimens with *Candida* antigen titers of ≥1:8 from patients with deep-seated candidiasis, 11 were from two patients with leukemia. Finally, unlike patient sera, the low *Candida* mannan antigen control did not have to be pretreated with detacher enzyme before being mixed with sensitized latex reagent. Latex agglutination with the low *Candida* mannan antigen control was not the result of no detacher enzyme treatment or of incomplete neutralization of enzyme activity. Both the low *Candida* mannan antigen control treated with detacher enzyme, with the reaction stopped by the addition of enzyme inhibitor or by boiling, and that left untreated reacted with the sensitized latex reagent. In fact, the enzyme-treated control agglutinated more strongly with the latex reagent than did the untreated sample.

The microbiological results showed that cultures may be helpful in laboratory diagnosis of disseminated candidiasis. For four of the six patients with disseminated disease, there was at least one set of positive blood cultures. For two of these patients, *C. albicans* grew in multiple sets of blood cultures. The possibility of a contaminated arterial line in these patients must be considered as a source of candidemia. Candidemia does not necessarily lead to deep-seated
Candida infections, although it is the most important route of Candida dissemination into deep tissues. Conversely, negative blood cultures should not be considered a criterion against deep-seated candidal infection. Data from a different study indicate that premortem candidemia is present in only 17 to 75% of the cases of disseminated candidiasis diagnosed postmortem (13).

Fungal surveillance cultures of urine, stool, and respiratory specimens have reportedly not been helpful in predicting systemic C. albicans disease (13). The surveillance study consisted of culturing samples from these body sites twice weekly and determining whether colonization at one of the sites correlated with systemic disease. With these criteria, only 7% of the patients persistently colonized with C. albicans for 2 or more weeks had systemic candidiasis (13). In our study, there was a difference in the number of body sites from which C. albicans was isolated in colonized patients versus those patients clinically diagnosed as having disseminated disease. C. albicans was recovered from three or four body sites in 75% of the patients with systemic disease, whereas the organism was recovered from one or two sites in 76% of the colonized individuals. The most frequent site from which C. albicans was isolated was the respiratory tract. The yeast was recovered from the mouth, sputum, bronchial washing, or throat or a combination of these sites in 16 patients, from urine specimens of 13 patients, from blood samples of 6 patients, from stool samples of 4 patients, and from other sites in 12 patients. A previous report suggested that the isolation of C. albicans from both stool and urine specimens most likely indicated disseminated candidiasis (2); in our study, however, patients 7 and 19 did not have systemic disease.

In conclusion, the latex agglutination test for circulating Candida antigens is useful in differentiating between C. albicans colonization and deep-seated infection. Rarely do uninfected or colonized patients have Candida protein antigen titers greater than 1:4. Since many of the patients in our series were immunosuppressed, this assay also appears to be useful for this patient population.

ACKNOWLEDGMENT

We acknowledge the assistance of Phyllis Schatz for the chart reviews of her patients included in this study.

LITERATURE CITED


