Utility of Fungal Blood Cultures for Patients with AIDS

Tim Mess and Eric S. Daar

From the Department of Medicine, Division of Infectious Diseases, Cedars-Sinai Medical Center, Los Angeles, California

This study was designed to define the clinical utility of fungal blood cultures for human immunodeficiency virus type 1–infected individuals. A retrospective chart review was performed for all patients admitted to an inpatient AIDS unit who had evidence of an invasive fungal infection. During a 25-month period, 1,162 fungal blood cultures were performed for 322 patients. These cultures, along with bacterial blood cultures, resulted in the isolation of fungi from 26 patients; 15 of these isolates were considered true pathogens. Routine blood cultures were positive for the fungal isolates in all 15 cases: Candida species and Candida glabrata (6 cases), Cryptococcus neoformans (7), Coccidioides immitis (1), and Histoplasma capsulatum (1). All invasive fungal infections were diagnosed by other means before fungal blood cultures were reported as positive. The results of this study suggest that the routine performance of such cultures in clinical practice should be reevaluated.

Patients with advanced HIV-1 infection present with an extended spectrum of infectious complications, including those due to a host of bacterial, mycobacterial, viral, parasitic, and fungal pathogens [1, 2]. Of the many infections associated with HIV disease, invasive fungal infections are relatively common and are usually considered in the initial diagnostic workup for febrile patients with <200 CD4⁺ T lymphocytes/mm³ [3]. Fungal blood cultures are labor intensive and expensive and represent only one of many tests that can result in the diagnosis of invasive fungal infection. Thus, to determine the clinical utility of fungal blood cultures for this patient population, we reviewed the results of these cultures for all HIV-1-infected patients admitted to an inpatient AIDS unit at our institution.

Patients and Methods

This study was a retrospective analysis of patients admitted to a 22-bed inpatient AIDS unit at Cedars-Sinai Medical Center between 1 July 1992 and 31 July 1994. Cedars-Sinai Medical Center is a 1,100-bed, university-affiliated, tertiary-care, teaching hospital in Los Angeles. On the basis of a review of 50 consecutive admissions of unique individuals during 1993, it was estimated that >90% of the patients admitted to this unit during the study interval fulfilled the 1987 Centers for Disease Control and Prevention surveillance case definition for AIDS [4]. All fungal cultures performed for patients admitted to this unit were evaluated. The medical records of all patients for whom fungal cultures were positive were reviewed for the following information: age, HIV-1-related diagnoses, hospital course, results of all bacterial and fungal blood cultures, symptoms and neutrophil count at the time of the positive culture, pertinent serological findings, fungal cultures of specimens other than blood, the most recent CD4⁺ T lymphocyte count, and the presence of a central venous catheter.

Routine blood cultures were performed by directly inoculating 5–10 mL of whole blood into BACTEC culture bottles (Becton Dickinson, Sparks, MD) at the bedside and subsequently analyzing them with use of the BACTEC 860 System (Becton Dickinson). These cultures were held for 5 days before being reported as negative. Fungal blood cultures were performed with use of a lysis centrifugation system where 10 mL of whole blood was directly aspirated into a DuPont isolator tube (Wampole Laboratories, Cranbury, NJ) and inoculated onto plates with Sabouraud brain-heart infusion agar and inhibitory mold agar. Fungal blood cultures were held for 21 days before being reported as negative. Positive fungal cultures were considered to be contaminants if there was only a single positive culture of an unusual pathogen (unlike Cryptococcus neoformans, Candida species, Coccidioides immitis, or Histoplasma capsulatum) and, most important, the patient’s condition improved without the initiation of specific antifungal therapy.

Results

There were 785 patients with 1,481 admissions to the inpatient AIDS unit between 1 July 1992 and 31 July 1994. A total of 1,162 fungal blood cultures were performed for 322 (41%) of the patients. Fungi were isolated from 62 fungal and/or routine bacterial blood cultures performed for 26 patients.

Of the 26 patients for whom blood cultures were positive for fungi, 15 were believed to have true infections (table 1). Routine bacterial cultures were positive for the fungal isolates in all 15 cases. Fungal blood cultures were performed for 12 of the 15 patients; all of these cultures were similarly positive. For the 12 patients for whom fungal blood cultures were positive, the first culture performed was positive for 10, while the
second culture performed was positive for two. For the three patients for whom fungal blood cultures were not performed and fungi were isolated only from routine bacterial cultures, the first set of cultures were diagnostic. None of the patients with fungemia were neutropenic, and all patients had advanced HIV disease.

Fungal blood cultures did not reveal any invasive fungal infections that were not also identified by routine bacterial cultures or cultures of specimens from other sites and/or by serological tests. Stains of CSF or bronchial washings and tests for serum cryptococcal antigen were positive for all patients with C. neoformans infection before any cultures were positive. Three of the four patients with infection due to Candida species and the two with Candida glabrata infection had central venous catheters; the one individual with infection due to Candida species who did not have such a catheter was known to have a history of candidemia at the time of admission. In addition, all of these fungi were isolated in bacterial blood cultures.

Although fungal blood cultures were not performed for the patient with H. capsulatum infection, there was pathological evidence of H. capsulatum in a bronchoscopic specimen before any blood cultures were positive and serological tests were confirmatory. Similarly, a sputum culture was positive and there was serological evidence of infection before blood cultures were positive for the patient with C. immitis infection. Despite the fact that the premortem diagnosis of invasive fungal infection was made for all the patients, and all patients, except the one with H. capsulatum infection who elected to receive only comfort measures, received amphotericin B therapy, seven died during hospitalization (table 1).

There were eight other patients admitted during this period for whom fungi were isolated from specimens other than blood: C. neoformans, was isolated from CSF (2 patients); C. immitis, from bronchoscopic specimens (2) and from a skin biopsy specimen (1); Aureobasidium, from bone marrow specimen (1); Paecilomyces, from a bone marrow specimen (1); and C. parapsilosis, from a bone marrow specimen (1). None of the patients for whom bone marrow cultures were positive had positive fungal blood cultures at the time that bone marrow cultures were performed. The two patients for whom C. neoformans was isolated from CSF did not have fungal blood cultures performed during hospitalization but did have positive assays for serum cryptococcal antigen. The two patients for whom C. immitis was isolated from the lung had positive serum titers; one had a negative fungal blood culture, and the other did not have any fungal blood cultures performed. The one patient for whom a skin biopsy specimen culture was positive for C. immitis had negative fungal blood cultures and no serological tests performed.

Fungal blood isolates from 11 patients admitted during the study period were considered contaminants. One culture each of 22 fungal and 32 bacterial blood cultures was positive for these individuals. None of these patients died during their hospitalizations. The presumed contaminants included the following: Penicillium (5), Acremonium (1), Cladosporium (1), Wangiella (1), Stemphylium (1), Aspergillus flavus (1), and Aspergillus fumigatus (1). Eight of the 11 patients had complete resolution of the symptoms for which they presented to the hospital despite receiving no antifungal therapy, while the conditions of three other patients (for whom the contaminants were Acremonium, Penicillium, and Wangiella) who were receiving chronic fluconazole therapy (also at the time that the cultures were performed) improved without alteration in therapy.

### Table 1. Blood culture results, serological findings, and clinical outcome for HIV 1–infected patients for whom fungi were isolated from at least one blood culture.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Organism</th>
<th>No. of positive blood cultures</th>
<th>Serological finding</th>
<th>Outcome for patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cryptococcus neoformans</td>
<td>ND 2 (2)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>C. neoformans</td>
<td>2 (2)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>C. neoformans</td>
<td>1 (1)</td>
<td>+</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>C. neoformans</td>
<td>2 (2)</td>
<td>+</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>C. neoformans</td>
<td>ND 2 (2)</td>
<td>+</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>C. neoformans</td>
<td>2 (2)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>C. neoformans</td>
<td>1 (1)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>Candida albicans</td>
<td>3 (3)</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>C. albicans</td>
<td>2 (2)</td>
<td>-</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>C. albicans</td>
<td>3 (5)</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>Candida glabrata</td>
<td>1 (1)</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>12</td>
<td>C. glabrata</td>
<td>2 (1)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>Candida parapsilosis</td>
<td>2 (1)</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>14</td>
<td>Coccioides immitis</td>
<td>5 (5)</td>
<td>-</td>
<td>Died</td>
</tr>
<tr>
<td>15</td>
<td>Histoplasma capsulatum</td>
<td>ND 1 (3)</td>
<td>+</td>
<td>Died</td>
</tr>
</tbody>
</table>

NOTE. NA = not applicable; ND = not done; + = presence of serum cryptococcal antigen, CF antibodies to C. immitis, or H. capsulatum polysaccharide antigen in urine.

Discussion

In this study, fungal blood cultures were of no value in the diagnosis of invasive fungal infections in HIV-1-infected individuals. In all cases, fungi were readily identified by serological tests, bacterial blood cultures, stains, and cultures of tissues, bodily fluid, or biopsy specimens. In fact, all 15 of the patients for whom fungi were isolated from blood had positive bacterial blood cultures. In addition, all serological tests that were performed for patients infected with C. neoformans, C. immitis, and H. capsulatum were positive. The invasive fungal infections in the eight patients for whom isolates were not recovered from blood were diagnosed by culture of tissue specimens or other bodily fluids.

Candida species and C. neoformans are the most frequently identified fungi causing the pandemic mycoses observed in patients with HIV disease [3]. In contrast, the possibility of
endemic mycoses such as those due to *C. immitis* and *H. capsulatum* is largely dependent on an individual’s recent and remote travel history [5, 6]. In addition, there are many other invasive fungal infections that have been identified less frequently in this patient population [7]. Since disseminated fungal infections generally occur in the advanced stages of HIV disease, fungal cultures are often ordered for febrile HIV-1-infected individuals. In order for the evaluation of such patients to be cost-effective, consideration must be given to the sensitivity and specificity of a given test as well as to the prevalence of each pathogen.

Our finding that invasive fungal infections can be diagnosed without fungal blood cultures is consistent with the observations of other investigators. In a smaller study of the diagnostic utility of fungal blood cultures, Katz et al. [8] similarly demonstrated that such cultures had little clinical value for febrile hospitalized patients with AIDS. These observations are largely due to the availability of other diagnostic studies [9–13] and to the fact that the BACTEC bacterial culture system is an effective means of isolating *Candida* species and *C. neoformans* [14, 15]. In addition, for cryptococcal disease, the test for serum cryptococcal antigen is rapid, highly sensitive (99%), and highly specific (97%) [9–11, 16].

Similar to cryptococcal disease, serological studies often result in the diagnosis of *H. capsulatum* and *C. immitis* infections. Although the yield of fungal blood cultures for the diagnosis of disseminated *C. immitis* infection in HIV-1-infected individuals is not known, if such cultures were employed as the sole means for diagnosing coccidioidomycosis in our center, two of the four cases would have been missed. The limited role of fungal blood cultures for this pathogen was further demonstrated by Ampel et al. [17]; these investigators showed that routine bacterial blood cultures were as sensitive as fungal cultures.

Los Angeles has a low prevalence of endemic mycoses such as those due to *H. capsulatum* and *Penicillium marneffei*, thus limiting our ability to draw conclusions from this study regarding the clinical utility of fungal blood cultures in diagnosing these infections. Another consideration is that our study exclusively included patients in the hospital, most of whom were in the advanced stages of HIV infection. It is possible that the results of a similar study in the outpatient setting could be different, and this possibility should be explored separately.

Another possible limitation in translating our experience to other institutions is differences in culture techniques. At the time of this study, our center utilized Dupont isolator tubes for fungal blood cultures, while many centers now use a BACTEC fungal system for these cultures. Differences in fungal culture methods are unlikely to effect the conclusions from our study. With the exception of *C. glabrata*, which grows equally well in either fungal culture system, studies have shown that both of the fungal culture systems are no better than the use of routine BACTEC medium for recovering *Candida* and *Cryptococcus* species [15, 17]. In contrast, the Dupont isolator tube has been shown to be superior to the BACTEC fungal system for culturing *H. capsulatum*.

In our study, *C. glabrata* was identified by routine cultures for both of the patients with infection due to this pathogen. Moreover, regardless of culture methods, the diagnosis of *H. capsulatum* infection is often made by rapid antigen assays. In fact, the reported sensitivity of culture for *H. capsulatum* for HIV-1-infected individuals is 83% [18], compared with a 93% sensitivity for *H. capsulatum* polysaccharide antigen (HPA) analysis [13]. For centers that send blood and urine samples away for standardized HPA analysis, the rapid turnaround time, along with the high sensitivity and specificity, makes cultures often a secondary method for diagnosis. In areas of endemicity, histoplasmosis is often diagnosed by HPA analysis alone [13]. In contrast, centers where the results of this assay are not available may rely more heavily on fungal cultures of blood.

The availability of highly sensitive and specific serological tests and the fact that many fungi grow in routine cultures suggest that blood cultures specific for fungi are of little diagnostic value for the most common fungal infections in HIV-1-infected patients [8, 19]. Although our study found no clinical utility for fungal blood cultures, two exceptions might be when infections with *H. capsulatum* or *C. glabrata* are suspected. Regardless, our study strongly argues that the performance of fungal blood cultures could be restricted to limited situations where the initial evaluation with other diagnostic studies remains unrevealing.

At a time when the cost of evaluating and treating patients with HIV disease is being scrutinized, every effort should be made to optimally utilize all resources. Fungal blood cultures resulted in an overall charge of $182,000 to patients admitted to our center during the 25 months of this study. This expense and the associated use of laboratory personnel resulted in 12 cultures with true-positive results for pathogens that had already been identified by pathological examination of specimens, serological tests, bacterial blood cultures, or cultures of other bodily fluids. These observations raise a serious question about the clinical utility of fungal blood cultures in the evaluation of febrile HIV-1-infected patients and should prompt larger prospective studies to definitively answer this very important question.

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**References**