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Performance of Fungal Blood Cultures by Using the Isolator Collection System: Is it Cost-Effective?

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Enhanced recovery of fungal isolates from blood by using the Isolator system has been reported previously. We examined bacterial and fungal blood cultures during a 14-month period to determine if this enhanced recovery required a separate fungal culture and to determine the differential utility between a fungal blood culture and a routine bacterial culture. During this period, 84 of 5,196 (1.6%) fungal blood cultures and 170 of 25,702 (0.6%) bacterial blood cultures were positive for yeast or filamentous fungi. Thirty-seven positive fungal cultures, simultaneously collected, had correspondingly positive bacterial cultures. An additional 15 positive fungal cultures yielded isolates that had either been previously recovered from a bacterial culture or were recovered from a bacterial culture collected within 48 h. Of the 32 unpaired fungal cultures remaining, 5 were *Candida albicans* whose unique isolation was believed to be the result of specimen sampling variance rather than any enhanced recovery characteristics of fungal culture methods. Examination of patient data relating to the 27 remaining isolates (24 patient episodes) showed that only five fungal blood cultures (0.096% of all collected) had any impact on patient therapy decisions, and one of these was judged to be the cause of unnecessary therapy. Our data suggest that separate fungal cultures of blood are not cost-effective for those laboratories using the Isolator for routine blood cultures and furthermore may not be cost-effective for laboratories using automated broth systems that are comparable to the Isolator in recovery of fungi.

In the early evaluation of the Isolator blood culture system, enhanced recovery of fungal isolates was reported (1, 4, 5). Our laboratory adopted Isolator for the performance of all blood cultures (bacterial, fungal, and mycobacterial) in 1989, replacing the BACTEC 460 radiometric system. While our routine inspection of culture data showed an increase in the number of fungal culture isolates, it was also observed that the recovery of fungal isolates from bacterial cultures had also increased, and in fact most fungal blood culture isolates were recovered first in bacterial cultures.

We sought to quantify this observation, determining the differential utility of a separate fungal blood culture. This utility can then be evaluated in light of the prolonged incubation of a fungal culture (3 weeks versus 5 days for a bacterial culture), the separate specimen and processing required for the fungal blood culture, and the typically less frequent examination schedule of fungal cultures.

MATERIALS AND METHODS

Routine bacterial and fungal blood cultures were collected in Isolator blood culture tubes and processed as follows.

Blood specimen volume was determined by comparison with premeasured tubes. Specimens from adults collected in the 10-ml Isolator tube that contained less than 5 ml of blood were not accepted for culture. Blood specimens were centrifuged at 3,000 × *g* for 30 min. The supernatant was aseptically removed and discarded from each tube. After vortexing, the sediment was then aseptically removed and divided evenly among appropriate media. During the study period, routine bacterial cultures were inoculated onto a 5% sheep blood agar plate, a sheep blood agar plate containing 0.001% pyridoxal hydrochloride, a chocolate agar plate, and brain heart infusion broth with vitamin K and hemin. Fungal blood cultures were inoculated onto three high-volume (40-ml) brain heart infusion agar plates.

Bacterial blood cultures were incubated at 35°C and inspected for growth twice daily for 5 days, and on the fourth day a subculture of the brain heart infusion broth was performed (on sheep blood agar and chocolate agar plates) and observed for an additional 2 days. Fungal blood culture plates were incubated at 30°C, inspected once daily for 7 days, and then examined every other day for an additional 2 weeks.

Culture results were entered into the SunQuest laboratory information system and then extracted into personal computer-maintained databases. Analysis of culture results was done using a relational database software package (dBase IV; Borland International, Inc., Scotts Valley, Calif.). Our analysis proceeded in four stages, the first of which was elimination of negative cultures.

Stage 2: elimination of redundant positive cultures. By examining the date and time of collection, we matched fungal blood cultures with simultaneously collected bacterial blood cultures. If a fungal blood culture isolate was also recovered from a contemporaneous bacterial blood culture, the fungal culture was considered redundant and removed from consideration. In addition, fungal cultures with prior bacterial cultures which grew the same fungal isolate or those with identically positive bacterial cultures collected within 48 h were eliminated from consideration.

Stage 3: elimination of *Candida albicans* isolates. *C. albicans* grows well on routine bacterial culture media. Our mean times to recovery of this isolate were similar to those in other published data and well within the bacterial culture incubation times. The unpaired *C. albicans* isolates recovered only from fungal blood cultures were considered products of specimen sampling variance and removed from consideration.

Stage 4: evaluation of clinical impact of remaining positive fungal cultures. Chart review for patients from whom the remaining positive fungal cultures were collected was performed by a physician (C.H.S.). Underlying condition, chart documentation or nondocumentation of positive fungal culture, and ultimate effect on therapy and/or management were noted.

RESULTS

Figure 1 graphically represents the analytical process. Starting with 5,196 fungal blood cultures, we immediately eliminated 5,112 (98.4%) which never grew any fungi.

When the remaining 84 positive cultures, described in Table 1, were then paired with the 25,702 routine blood cultures collected during the same period, 37 were eliminated because a simultaneous bacterial blood culture grew the same fungal isolate. Fifteen additional isolates were eliminated because a previously collected bacterial blood culture grew the fungal isolate or because the fungal isolate grew in a bacterial culture

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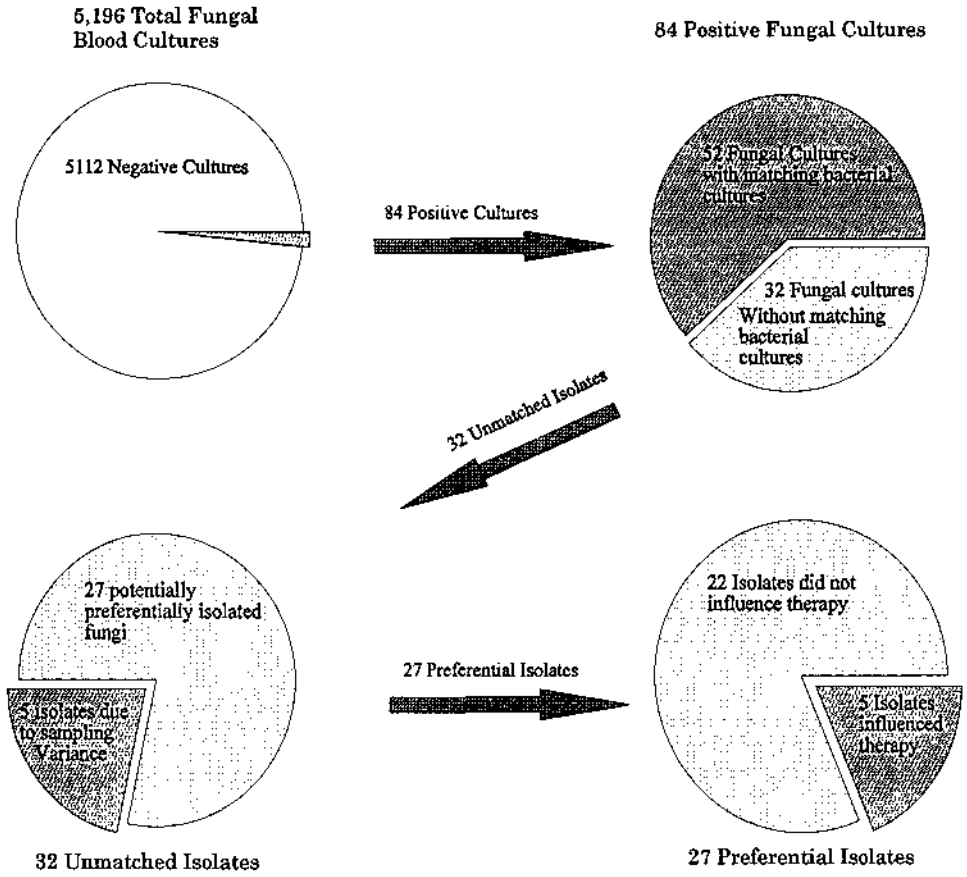

FIG. 1. Diagram depicting the analytical process for fungal blood cultures.

TABLE 1. Characterization of 85 fungal isolates from 84 blood cultures

Species	No. of isolates		
	Total	Unmatched	Which affected therapy
Candida glabrata	24	5	0
Candida albicans	18	0	0
Cryptococcus neoformans	9	0	0
Candida parapsilosis	7	2	1
Candida krusei	4	2	1
Fusarium sp.	3	3	0
Candida tropicalis	3	1	0
Cladosporium sp.	3	3	0
Saprophytic species[a]	2	2	0
Rhodotorula rubra	2	1	1
Penicillium sp.	2	2	1
Paecilomyces sp.	2	2	0
Aspergillus flavus	2	1	0
Trichosporon pullulans	1	1	0
Trichosporon beigelii	1	0	0
Cryptococcus albidus	1	1	1
Aureobasidium sp.	1	1	0
Total	85	27[b]	5

[a] Filamentous fungi without fruiting bodies, i.e., sterile septate hyphae.
[b] From 24 patients.

collected within the subsequent 48 h. Ninety-seven bacterial pathogens were also recovered from fungal blood cultures, of which 64 were never recovered from routine bacterial cultures. This is typical of the specimen sampling phenomenon mentioned below.

Of our 32 remaining isolates, 5 were low-quantity isolations of the yeast *C. albicans*. As noted by Geha and Roberts (3), this species grows well on the media used for routine bacterial blood cultures, so their unmatched isolation is therefore not attributable to the specialized media of fungal cultures. Our average time to positivity for *C. albicans* in routine bacterial blood cultures is 1.8 days, with 95% of *C. albicans* isolates becoming positive by day 3, well within the 5-day incubation period for routine bacterial cultures. By contrast, the two other most common yeasts in the list, *Candida glabrata* and *Candida parapsilosis*, have average times to positivity of 2.7 and 2.5 days, respectively, with only 75 and 79%, respectively, of the isolates recovered by day 3. This slower growth pattern for these species was also noted by Geha and Roberts (3). It is apparent, then, that the unmatched *C. albicans* isolates were the result of specimen sampling variance, as were the unmatched bacterial isolates recovered from fungal blood cultures; we therefore removed them from consideration. While sampling variance may have accounted for lone isolations of *C. glabrata* and *C. parapsilosis* as well, we chose not to exclude them from consideration on the basis of their slower growth patterns.

Thus, the 27 remaining unmatched cultures (from 24 patients) were not recovered in bacterial cultures and grew isolates that might justify separate fungal blood cultures.

Examination of the hospital records of these 24 patients revealed a relatively narrow range of underlying disease processes. Nineteen were oncology or bone marrow transplant patients, four were patients with severe chronic illness, and one patient episode was associated with a brief acute illness.

Only 10 of the 24 patients had a positive fungal culture(s) documented on their charts. Of the 14 remaining, 10 were still in the hospital at the time of the positive culture and 4 had been discharged or had died before the culture became positive.

Eighteen of the 24 patients received antifungal therapy before and after the culture became positive. Only three of these had any indication of prolongation of therapy due to the positive culture. Four patients received no antifungal therapy before or after the culture became positive. For three of these patients there was no evidence in the chart of any effect on management of care as a result of the positive cultures. The fourth patient who received no antifungal therapy before or after the culture became positive had additional fungal blood cultures (all negative) collected after the positive culture. Two patients were begun on antifungal therapy because of the positive cultures. The therapy for one of these patients was discontinued after the fungal isolate was identified as a *Penicillium* strain and deemed a contaminant.

Thus, only five patients were found to have had therapy that was affected by the positive culture results (two therapy initiations and three therapy prolongations). A summary of these five patient cases follows.

Case 1. A 66-year-old female with metastatic breast cancer was started on fluconazole when a blood culture grew fungus, with recognition that the isolate could be a contaminant. Antifungal therapy was discontinued when fungus was identified as a *Penicillium* strain.

Case 2. A 66-year-old female with acute myelogenous leukemia undergoing chemotherapy had neutropenic fever and was placed on antifungal therapy when a culture grew *Candida krusei* 3 days after a febrile spike.

Case 3. A 46-year-old female with acute myelogenous leukemia, status post-bone marrow transplant, was placed on amphotericin empirically for a febrile spike occurring during the course of broad-spectrum antibacterial therapy. A fungal blood culture grew *Rhodotorula rubra* 14 days later, causing antifungal therapy to be prolonged.

Case 4. A 49-year-old male with non-Hodgkin's lymphoma, status post-bone marrow transplant, was placed empirically on broad-spectrum antibiotic therapy including fluconazole after a febrile spike. A second febrile spike 48 h later prompted addition of amphotericin B therapy. A fungal blood culture collected at the time of the first febrile spike, before antifungal therapy had been started, grew *C. parapsilosis* 8 days after collection. The patient was improving clinically, but the positive culture was specifically cited as a rationale for extension of amphotericin therapy for the duration of the hospital stay and following discharge, via daily visits to a clinic, until a 1-g total dose was achieved.

Case 5. A 28-year-old female with chronic granulomatous leukemia, status post-bone marrow transplant, was on broad-spectrum antibacterial therapy as well as amphotericin prophylaxis when a fungal blood culture recovered *Cryptococcus albidus*. Amphotericin therapy was continued, and the vascular device through which the blood culture had been collected was removed. The patient died a month later of *C. glabrata* enteritis and sepsis.

DISCUSSION

The unique and preferential recovery of only five fungal isolates which prompted a change in therapy out of 5,196 cultures suggests that separate processing of blood specimens for fungi is not cost-effective. Of course, retrospective analysis is only part of the overall evaluation of the utility of a laboratory test. In general terms the effectiveness of a laboratory test can be analyzed according to four variables.

(i) The fraction of tests that produce significant new information. In the case of cultures, the fraction of tests producing significant new information can be viewed as the pathogen recovery rate. The cost of detection of a pathogen can be calculated by dividing the total cost of all fungal blood cultures by the number that were positive for a pathogen. Clearly, if a culture is very seldom positive, the cost absorbed by the laboratory and, in turn, the patients with negative tests, to detect a pathogen is very high. In our laboratory, the cost of detection of a pathogen in bacterial blood cultures is approximately $745. The cost of detection of a pathogen in mycobacterial blood cultures is approximately $500. The very low positivity rate of fungal cultures in this study increases their cost of detection to over $4,700.

(ii) The turnaround time of the test. It is important that the laboratory provide test information while that data can benefit the patient's condition and therapy. While the indolent nature of some fungal infections may afford the laboratory time to recover an isolate, the extended incubation can be problematic for the physician in the case of negative cultures. Physicians often wait until a negative culture has been held for the full incubation period before discontinuing therapy begun empirically at the time of culture collection. Our routine bacterial blood cultures were held for 5 days, well within the duration of normal antibacterial regimens for sepsis (10 to 14 days). Mycobacterial cultures, while requiring 6 weeks to process, are still shorter than the treatment regimen, which can be 6 months to a year. The 21-day incubation period for fungal cultures, however, approximately matches the duration of antifungal therapy. The decreased utility of this prolonged turnaround time can be seen in the case of a physician seeking to discontinue antifungal therapy started at the time of culture and subsequently thought to be unneeded. Because of the 3-week incubation period, the physician will not have the final documentation of a negative culture and may be reluctant to prematurely stop therapy. The final confirmation of the negative culture will coincide with the routine discontinuation of therapy.

(iii) The differential value of the test. Any laboratory test must be able to add value over other available diagnostic means, either by providing unique information or through superior differential performance. In this case, very little value is added by the differential performance of a fungal versus a bacterial culture. Furthermore, for bacterial cultures, one important added value is the ability to perform therapeutically specific susceptibility testing. For fungal cultures, this is of limited usefulness because fungal susceptibility testing is not sufficiently standardized and is not routinely performed in most laboratories.

(iv) Potential harm of false positives. Among the charts reviewed, a fungal contaminant prompted at least one unnecessary treatment with antifungal agents. Because some antifungal agents have significant side effects, the risk from false positives is high. Telenti and Roberts (8) reported that as many as 17% of candidemias may represent contamination. We have observed yeast, including *C. parapsilosis*, contaminating blood cultures in our laboratory. Thus, it is likely that the number of

false-positive fungal blood cultures is higher than documented by the chart review. In the patient population most often associated with fungal blood cultures, namely, the immunocompromised, it can be very difficult for a physician to discern whether an isolate is a contaminant, therefore making unnecessary therapy likely.

Notably absent from our culture database were isolates of *Blastomyces*, *Coccidioides*, or *Histoplasma*, which typically require extended incubation times. Our recovery rates for most fungi were very similar to those reported by Wilson et al. (9) except for the lack of *Histoplasma* isolates. In regions and institutions where these organisms are seen more often, fungal blood cultures may be justified. Morris et al. (7) recently suggested that a similar distinction be considered for extended incubation of fungal cultures.

Our institution performs Isolator cultures for both bacterial and fungal cultures. Laboratories using other culture methods will have to evaluate the fungal recovery rates of their bacterial and fungal systems. However, the questionable utility of fungal blood cultures indicated by the overall low recovery rate can be considered regardless of laboratory methods. In addition, recent reports have suggested that other culture systems are now approaching Isolator's fungal recovery rates (2, 9). If so, our conclusions may become completely transferable.

Prompted by our preliminary analysis of fungal blood culture data (6), the hematology-oncology services at our hospital reevaluated their fungal culture ordering protocols. As a result, the number of fungal blood cultures ordered dropped from a monthly average of 420 to 82. This reduction in fungal blood cultures produced a cost saving of more than $300,000 annually.

Our analysis indicates that fungal blood cultures are not a cost-effective test. The amount, type, and timing of test results add relatively little to the medical process. While there are cases and/or local variation in epidemiology that might require fungal blood cultures, their general usage should be restricted.

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