JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1984, p. 126–128
0095-1137/84/020126-03$02.00/0

Vol. 19, No. 2

Clinical Evaluation of the Lysis-Centrifugation Blood Culture System for the Detection of Fungemia and Comparison with a Conventional Biphasic Broth Blood Culture System

JACQUES BILLE,† RANDALL S. EDSON, AND GLENN D. ROBERTS*

Department of Laboratory Medicine, Section of Clinical Microbiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905

Received 29 August 1983/Accepted 1 November 1983

In a comparative fungal blood culture study, a lysis-centrifugation system (Isolator; Du Pont Co., Wilmington, Del.) detected 89% of all episodes of fungemia; the lysis-centrifugation system detected fungemia exclusively or significantly earlier than did a biphasic brain heart infusion bottle system 83% of the time. The lysis-centriguation system was particularly useful in the early detection of fungemia caused by *Candida tropicalis* and *Candida glabrata*. In 53% of the clinically significant episodes, the earlier detection was directly helpful in the management of patients with fungemia. High-magnitude candidemia (>5 CFU/ml of blood) was significantly associated with the presence of an infected intravascular catheter and with *Candida* species other than *Candida albicans*. The lysis-centrifugation system was sensitive in the detection of fungemia during the monitoring of patients receiving antifungal agents or after removal of an infected intravascular catheter.

Systemic fungal infections are seen with increasing frequency in compromised hosts. Major risk factors include the administration of broad-spectrum antibiotics, corticosteroids, or cytotoxic drugs; intravascular catheters; total parenteral nutrition; and major surgical procedures.

The recovery of fungi from blood is an insensitive marker of disseminated fungal disease. However, the use of vented blood culture bottles and biphasic media has considerably increased the recovery rate and decreased the recovery time of fungi from blood (1, 7). Nevertheless, many disseminated fungal infections either remain undetected or are detected too late to beneficially affect patient management.

A lysis-centrifugation (LC) system is available for blood cultures (5). Compared with a conventional broth culture system, the LC system has provided a higher detection rate and shorter detection time of fungemia (4). We recently reported a 36.6% increase in the detection of fungemia by the LC system as compared with conventional biphasic brain heart infusion (BHI) broth agar-slant blood culture (2).

The present report assesses the clinical significance of earlier and more sensitive detection of fungemic episodes. Because the LC system provides a quantitative measure of fungemia, we correlated the initial colony counts with clinical parameters, host factors, response to antifungal therapy, and patient outcome. We also assessed the value of the LC system as a means to quantitatively monitor the effect of antifungal therapy or removal of infected intravascular catheters or both.

MATERIALS AND METHODS

The Isolator (Du Pont Co., Wilmington, Del.) was compared with the biphasic BHI bottle as previously described (2).

For each patient with positive blood cultures by the BHI biphasic bottle or the Isolator, the following information was recorded: age, sex, length of hospitalization, presence and type of underlying disease(s), degree of immunosuppression, prior surgery, prior antibiotic therapy or antimicrobial prophylaxis, previous episode(s) of bacterial sepsis, presence of intravascular catheters, and administration of parenteral nutrition. To evaluate the clinical significance of each episode of fungemia, we considered the following parameters; number of positive blood isolates per episode; number of consecutive days of documented fungemia; recovery of the same organism from sites other than blood; presence of fever, chills, and disseminated lesions (cutaneous or retinal); clinical deterioration without alternative explanation; attending physician's evaluation; response to therapy; and outcome. To be considered clinically significant, fungemia had to be documented from at least two separate blood cultures. The blood culture system was considered clinically useful in the presence of at least one of the following conditions: (i) antifungal therapy initiated before the comparative system became positive, (ii) intravascular line removed before the comparative system became positive (catheter positive for the same organism), (iii) culture positive only by one system and considered clinically significant. Relevant clinical and laboratory data were correlated with the magnitude of fungemia and with the results of subsequent quantitative blood cultures. The effect of antifungal therapy or intravascular catheter removal was correlated with serial quantitation of follow-up blood cultures and with clinical outcome.

RESULTS

Table 1 lists the number of patients with positive fungal blood culture(s) detected by either or both systems. Of 35 episodes, 29 (83%) were detected by the LC system alone or earlier than by the BHI system. Of the 35 episodes, 5 (14%) were detected by the BHI system alone or earlier than by the LC system ($P < 0.01$).

Table 2 shows the episodes of fungemia divided into two groups, those clinically significant (86%) and those deemed clinically insignificant (14%). Among clinically significant episodes, early detection was considered directly useful in

* Corresponding author.
† Present address: Antenne de Microbiologie, BH, Centre Hospitalier Universitaire Vaudois, CH-1011, Lausanne, Switzerland.

TABLE 1. Initial detection of fungemia

Organism	No. of episodes of fungemia[a]	No. detected first (no. detected only) by:		P
		Isolator	BHI	
Candida albicans	11	7 (3)	4 (3)	NS[b]
Candida tropicalis	6	6 (3)	0	<0.05
Candida glabrata	10	9 (2)	1 (1)	<0.05
Candida parapsilosis	2	2 (1)	0	
Candida guillermondii[c]	1	0	0	
Cryptococcus neoformans	2	2	0	
Trichosporon beigelii	1	1	0	
Histoplasma capsulatum	3	3	0	
Beauveria species	1	1	0	

[a] There were 35 different patients; 1 patient had *C. albicans* and *C. glabrata* fungemia, and 1 patient had *C. albicans* and *C. parapsilosis* fungemia. A total of 29 (83%) patients had fungemia detected by the LC system alone or earlier than the BHI system; 5 (14%) patients had fungemia detected by the BHI system alone or earlier than by the LC system ($P < 0.01$).

[b] NS, Not significant.

[c] Episode detected at the same time by both systems.

patient management in 17 of 30 instances (57%). The clinically insignificant episodes were all detected by one system alone (LC system, three episodes; BHI system, two episodes), and those detected by the LC system were all of very low magnitude (0.1 CFU/ml of blood).

Table 3 shows a comparison of several clinical parameters according to the magnitude of candidemia present at the time of the initial detection. Low-level candidemia was defined as <5 CFU/ml of blood or <50 colonies per culture; high-level candidemia was defined as >5 CFU/ml of blood or >50 colonies per culture. High-level candidemia was significantly associated with the presence of an infected intravascular catheter in 10 patients, and 90% were related to *Candida* species other than *Candida albicans*. These included the following species (number of episodes): *Candida parapsilosis* (1), *Candida tropicalis* (2), *Candida glabrata* (5), and *Candida guilliermondii* (1). The magnitude of fungemia was not associated with the administration of antifungal therapy or patient outcome.

Results of blood cultures obtained by both systems after initiation of antifungal therapy or removal of an infected intravascular catheter or both were compared in 12 patients. Of the 27 cultures taken, the LC system detected 96.7% of the positive cultures and 100% of the episodes of fungemia, whereas the BHI biphasic system detected 33% of the positive cultures and 42% of the episodes of fungemia.

TABLE 2. Clinical significance and usefulness of detection of fungemia by one system alone or earlier

Type of episode (no.)	No. of episodes detected by:			
	Isolator		BHI	
	Only	Earlier	Only	Earlier
Clinically significant (30)[a]	5	21	2	1
Clinically insignificant (5)	3	0	2	0
Directly useful for patient[b]	3	13	1	0

[a] One clinically significant episode was detected at the same time by both systems.

[b] Among the clinically significant episodes only.

DISCUSSION

Most blood culture studies are limited to an analysis of the number and the types of different organisms recovered from blood. Analysis on a patient-by-patient basis eliminates the bias given by an uneven number of samples drawn from different patients. In the present study, 89.6% of the cases of clinically significant fungemia were detected by the LC system; 17% of them were detected by this system only, and 70% were detected at least 1 day earlier than by the conventional BHI system. Earlier detection of fungemia or bacteremia does not necessarily translate into direct patient benefit. In the present study, however, therapeutic measures were undertaken on the basis of a positive LC culture only in 53.3% of the cases, making the LC system a clinically useful tool in patient management. Conversely (Table 2), the BHI system was found to be clinically useful in only 3.3% of the episodes of fungemia.

Quantitative blood cultures have received some attention mainly in the pediatric literature and have dealt almost exclusively with bacteremia (3, 8, 9). The magnitude of fungemia is not extensively established. Cases in which fungi are detected in a buffy-coat or direct blood smear are infrequent and attest to the occasional presence of a high number of circulating organisms. Quantitative fungal blood culture data gathered by Hill et al. (6) suggest a wide range in the number of *Candida* spp. and *Cryptococcus neoformans* organisms recovered from blood. Our data confirm and extend this observation and suggest that there is no clear-cut relation between the initial magnitude of fungemia and the clinical significance of the episode; however, all positive cultures considered clinically insignificant were of very low magnitude.

More importantly, high-magnitude candidemia was found to be significantly associated with the presence of an infected intravascular catheter; if this association is further confirmed, the therapeutic approach of patients with candidemia might be altered by the knowledge of the magnitude of fungemia. In particular, patients with surgically implanted intravascular catheters and low-level fungemia might be treated with antifungal agents without removal of the catheter and closely followed by successive LC-processed blood cultures.

Of interest are three episodes of fungemia with very high initial colony counts which occurred in splenectomized patients. To our knowledge, splenectomy has not been

TABLE 3. Correlation of magnitude of candidemia to clinical parameters

Type of episode (no.)	Degree of fungemia		P[a]
	Low grade (<5 CFU/ml)	High grade (>5 CFU/ml)	
Candidemia detected by Isolator (23)	12	11	NS
Clinically significant (20)	9	11	NS
Clinically insignificant (3)	3	0	
Catheter associated (10)	0	10	<0.01
Non-catheter associated (10)	9	1	
Species related	6	1	<0.02
C. albicans (7)	3	10	
Non-*C. albicans* (13)			

[a] Fisher's exact test. NS, Not significant.

correlated with overwhelming fungemia. From a practical standpoint, in four cases of high-level candidemia, the organisms were seen in a direct stain (acridine orange stain) prepared from the sediment of the LC tube at processing time. However, only ca. 1,000 tubes were examined in this fashion during the study, and these observations suggest the potential value of a direct smear of blood culture material in selected clinical situations and establish a need for this type of evaluation. The usefulness of the LC system as a means of monitoring the response to the administration of systemic antifungal agents is suggested by our data on positive cultures taken while the patients were on therapy. The LC system appears to be more sensitive than the conventional method to evaluate the response to therapy. The quantitative rate of response after removal of infected intravascular devices might be used to determine both the necessity and duration of antifungal therapy.

LITERATURE CITED

1. **Bille, J., G. D. Roberts, and J. A. Washington II.** 1983. Retrospective comparison of three blood culture media for the recovery of yeasts from clinical specimens. Eur. J. Clin. Microbiol. **2**:22–25.
2. **Bille, J., L. Stockman, G. D. Roberts, C. D. Horstmeier, and D. M. Ilstrup.** 1983. Evaluation of a lysis-centrifugation system for the recovery of yeasts and filamentous fungi from blood. J. Clin. Microbiol. **18**:469–471.
3. **Dietzman, D. E., G. W. Fischer, and F. D. Schoenknecht.** 1974. Neonatal Escherichia coli septicemia—bacterial counts in blood. J. Pediatr. **85**:128–130.
4. **Dorn, G. L., G. A. Land, and G. E. Wilson.** 1979. Improved blood culture technique based on centrifugation: clinical evaluation. J. Clin. Microbiol. **9**:391–396.
5. **Dorn, G. L., and K. Smith.** 1978. New centrifugation blood culture device. J. Clin. Microbiol. **7**:52–54.
6. **Hill, J. M., Y. Lemeshev, and A. S. Pardue.** 1981. Septicemia: early pure isolate and quantitation. A new blood culture method. J. Clin. Hematol. Oncol. **11**:3–17.
7. **Kiehn, T. E., C. Capitolo, J. B. Mayo, and D. Armstrong.** 1981. Comparative recovery of fungi from biphasic and conventional blood culture media. J. Clin. Microbiol. **14**:681–683.
8. **La Scolea, L. J., Jr., D. Dryja, T. D. Sullivan, L. Mosovich, N. Ellerstein, and E. Neter.** 1981. Diagnosis of bacteremia in children by quantitative direct plating and a radiometric procedure. J. Clin. Microbiol. **13**:478–482.
9. **Santosham, M., and E. R. Moxon.** 1977. Detection and quantitation of bacteremia in childhood. J. Pediatr. **91**:719–721.