Controlled Comparison of BacT/ALERT FAN Aerobic Medium and BACTEC Fungal Blood Culture Medium for Detection of Fungemia

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Yeasts are an increasingly common cause of nosocomial bloodstream infections. Methods for their detection are many; controlled comparisons are few. The vented FAN aerobic blood culture medium has been shown to be superior to the standard BacT/ALERT aerobic medium for the detection of fungemia as well as bacteremia. The BACTEC selective fungal medium (FM) (BD Biosciences, Sparks, Md.) allowed detection of more episodes of fungemia than did a resin-containing medium with equal volumes of blood cultured. Therefore, we compared vented FAN to FM for the ability to recover fungi from the blood of patients who were at increased risk of having fungemia. From 5,109 cultures processed for which both FAN and FM bottles were adequately filled, fungi were recovered from 87 cultures. Of these, 47 were detected with both bottles, 12 were detected with FAN only, and 28 were detected with FM only ($P < 0.05$). FAN was the first bottle positive for 36 of the 47 cultures for which both bottles yielded the same fungus, whereas the FM bottle was the first bottle positive for 11 cultures ($P < 0.001$). A total of 54 episodes of fungemia were identified, with 40 detected by both media, 4 detected only by FAN, and 10 detected only by FM (P value, not significant). We conclude that the vented FAN aerobic bottle is comparable to the FM bottle for detection of episodes of yeast infection but has the added benefit of detecting bacteria.

Fungemia is a frequent complication in immunosuppressed and other severely ill hospitalized patients. This condition, like bacteremia, is responsible for significant morbidity and mortality in the modern tertiary care setting (1, 9). Specialized systems or media that promote the recovery of fungi from blood cultures have been developed. Although not specifically designed for the recovery of fungi alone, lysis-centrifugation (LC) is a nonautomated method in which blood is lysed and centrifuged for plating on various solid media (3). The BACTEC fungal medium (FM) is a specialized medium designed for use with the BACTEC NR 660, 730, and 860 blood culture instruments (Becton Dickinson, Microbiology Systems, Sparks, Md.). This medium contains chloramphenicol and tobramycin to suppress bacterial growth and a lysing agent to cause hemolysis and release of phagocytized fungi. In a multicenter comparative study done at four university-affiliated hospitals (12), the FM bottle was found to be equivalent to the 10-ml Isolator LC blood culture system (Wampole Laboratories, Cranbury, N.J.), with the exception of detection of *Histoplasma capsulatum*, and superior to the BACTEC Plus 26 nonradiometric bottle for the detection of fungemia.

Another approach to the enhanced detection of fungemia has been the design of media with improved yields of both bacteria and fungi. The BacT/ALERT (Organon Teknika Corp., Durham, N.C.) continuously monitoring blood culture system using standard Trypticase soy broth-based media has been shown to provide equivalent yields and earlier detection times of positive blood cultures growing bacteria and yeasts in comparison with the BACTEC 660/730 nonradiometric blood culture system (13). The original formulation of the vented FAN aerobic medium, a brain heart infusion broth-based medium containing a proprietary substance termed Ecosorb (Fuller's earth and activated charcoal), provided improved yields of fungi and bacteria (10) compared with standard aerobic medium in a multicenter comparative study. A medium with equivalent yields for both bacteria and fungi in the same bottle could provide improved efficiency and reduced cost. We therefore compared FAN to FM for the ability to recover fungi from the blood of patients who were at increased risk of having fungemia (1).

MATERIALS AND METHODS

Patient selection. Patients at increased risk for having fungemia were evaluated at Duke University Medical Center (DUMC), Robert Wood Johnson University Hospital, and the Salt Lake City Veterans Affairs Medical Center. At each of the study sites, patient care areas were identified where the isolation rate of fungi from blood cultures was greater than isolation rates in other patient care locations. These locations were supplied with study blood culture kits for routine and/or fungal blood cultures from all patients. At a site where specialized fungal blood cultures had been available prior to the study (DUMC), the study kits were also used hospital-wide for fungal blood cultures when ordered specifically.

Collection and processing of samples. Blood for culture was obtained at the patient's bedside after preparation of the skin with 10% povidone–iodine fol-

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TABLE 1. Comparative yields of clinically important fungi in FAN and FM bottles

Fungus or isolate group	No. of isolates recovered by:			P value
	Both bottles	FAN only	FM only	
Candida albicans	19	1	7	NS
Candida krusei	1	0	0	
Cryptococcus neoformans	2	0	3	
Candida parapsilosis	1	0	2	
Candida tropicalis	12	4	4	
Candida famata	1	1	0	
Candida glabrata	11	6	11	NS
Fusarium sp.	0	0	1	
All fungi	47	12	28	<0.05
Therapy (%)[a]	8 (17)	3 (12)	5 (18)	NS

[a] Recovered from cultures drawn while patients were on theoretically effective therapy.

TABLE 3. Comparative detection of episodes of fungemia in FAN and FM bottles

Fungus or episode type	No. of episodes detected by:			P value
	Both bottles	FAN bottle	FM bottle	
Candida albicans	11	0	3	
Cryptococcus neoformans	2	0	1	
Candida tropicalis	6	1	0	
Torulopsis candida	1	0	0	
Candida glabrata	7	2	3	NS
Fusarium sp.	0	0	1	
Polymicrobial[a]	13	1	2	NS
All fungi	40	4	10	NS

[a] At least one microorganism of a polymicrobial episode was a fungus detected by one or both bottles.

lowed by 70% isopropyl alcohol. Blood (25 ml) from each separate venipuncture was distributed as follows: 10 ml to one FAN bottle, 10 ml to one FM bottle, and 5 ml to one BacT/ALERT standard anaerobic bottle. To ensure that the culture bottles were inoculated with the specified volume of blood, we measured the level of fluid in each container after it was filled with blood. Although all blood-containing bottles were incubated and processed for patient care, only bottle pairs (FAN and FM) that met volume standards were included in the subsequent analysis. An adequately filled bottle pair included each bottle filled with 8 to 12 ml of blood.

Identical methods were used to process blood cultures in the clinical microbiology laboratories at all study sites. All bottles were placed on either the BacT/ALERT (FAN and standard anaerobic bottles) or the BACTEC 660 (FM bottles) instruments and incubated for up to 14 days. All FAN bottles were vented prior to loading in accordance with the manufacturers' recommendations. For all FM bottles, growth value readings were taken twice daily for the first 2 days, once daily on days 3 through 7, and once daily on days 11 and 14. When growth was detected, all microorganisms were identified by standard microbiological procedures (7). Each bottle was treated independently, and only bottles flagged as positive by the instruments were processed further. Negative bottles that were companions to bottles that were flagged as positive and yielded fungi were subcultured.

Clinical assessment. A physician who specialized in infectious diseases reviewed positive cultures. The microorganisms isolated were judged on the basis of published criteria (11) to be the etiologic agents of bacteremia and fungemia, contaminants, or indeterminate as the cause of sepsis. Evaluations were also made as to whether the patient was receiving antimicrobial therapy at the time the culture was drawn and whether such therapy was likely inhibitory to the organism recovered from the culture.

Analysis of data. Only adequately filled pairs of FAN and FM bottles that grew microorganisms judged to represent true bacteremia or fungemia were compared. For the episode analysis, inadequately filled bottles were also used to help delineate the duration of episodes. An episode of bacteremia or fungemia was

defined as the period beginning on the date when the first positive blood culture was drawn and continuing for 7 days after the date of the last blood culture positive for the same organism. If another blood culture drawn within this time period grew the same organism as the most recent positive blood culture, then the later isolation was considered part of the same episode. If, however, a culture yielding the same organism was drawn more than 7 days from the last positive culture, then the later isolation was considered a new episode. If a different microorganism isolated from a patient grew from cultures drawn within 72 h of the time of cultures yielding the first isolate, then both isolates were considered part of a single polymicrobial episode. If, however, a different organism isolated from a patient grew from cultures drawn more than 72 h after the time of the first isolation, then the second isolate was considered as representing a second episode. Comparisons were evaluated statistically by either the Student *t* test or the modified chi-square test described by McNemar (6), with the Yates correction used when appropriate for small numbers of observations.

RESULTS

A total of 5,109 adequately filled bottle pairs were received during the study period. Of these, 636 (12%) were positive, including 445 (9%) that grew 496 microorganisms that caused illness, 175 (3%) that grew one or more contaminants, and 16 (0.3%) that grew one or more microorganisms that were indeterminate as a cause of sepsis. A total of 87 fungi were recovered from 83 cultures, with 47 detected by both bottles, 12 detected by FAN only, and 28 detected by FM only ($P < 0.05$) (Table 1). FAN was the first bottle positive for 36 of the 47 cultures for which both bottles yielded the same fungus, whereas the FM bottle was the first bottle positive for 11 cultures ($P < 0.001$) (Table 2). The average time to detection among cultures with both bottles positive within 5 days of incubation was 34.6 ($\pm$17.9) h for the FAN bottle and 43.7 ($\pm$24.3) h for the FM bottle ($P < 0.05$). Overall, there were only two FM bottles positive for fungi (*Cryptococcus neoformans*, detected only by FM, and *Candida parapsilosis*, detected by both FM and FAN) after 5 days of incubation, whereas no FAN bottles yielded a fungus after 5 days of incubation. In only one instance, that of an isolate of *C. neoformans* recovered by subculturing of a FAN bottle, was a fungus detected by terminal subculture that was not detected during the period of incubation on the instrument. There were a total of 54 episodes of fungemia (including polymicrobial episodes), with 40 detected in both media, 4 detected only by FAN, and 10 detected only by FM (P = not significant [NS]) (Table 3).

Of 376 adequate positive cultures, physicians at one of the study centers (DUMC) had specifically ordered 110 cultures as

TABLE 2. Comparison of speed of detection of clinically important fungi in FAN and FM bottles

Fungus	No. of isolates detected first in:		P value
	FAN bottle	FM bottle	
Candida albicans	13	6	NS
Candida krusei	1	0	
Cryptococcus neoformans	2	0	
Candida parapsilosis	1	0	
Candida tropicalis	11	1	<0.01
Candida famata	0	1	
Candida glabrata	8	3	NS
All fungi	36	11	<0.001

fungal blood cultures. Among these were 19 (17%) cultures that grew fungi, 90 (82%) that grew bacteria, and 1 (1%) that grew both yeast and bacteria. Of the remaining 266 positive cultures not ordered specifically as fungal blood cultures, 39 (15%) were positive for fungi, 217 (82%) yielded bacteria, and 10 (4%) yielded both fungi and bacteria.

DISCUSSION

For almost two decades, the LC system has been viewed as the optimal system for recovery of fungi from blood (2). Wilson et al. showed in a volume-controlled, multicenter study that the FM medium studied here matched the performance of LC for recovery of yeasts from blood. The need for a special blood culture system for fungi, however, has also been questioned based both on absolute costs and on costs for incremental yield. Petti et al. (8) could show no difference in practice between detection of fungemia in children by LC and that by a standard aerobic medium.

The theoretical advantage of the selective FM medium is the suppression of bacterial overgrowth (because of chloramphenicol and tobramycin in the medium) that would interfere with the growth of any yeasts present in the sample (4). There are at least two flaws in this approach. First, clinicians cannot tell a priori whether yeasts or bacteria will be present in a septic patient. This was shown in earlier work (12) and again in this study, in which 82% of patients thought to be at risk for fungemia had only bacteria isolated. The second pitfall is that all blood cultured in the selective FM bottle is blood that is wasted with regard to isolation of the more common bacterial pathogens inhibited by the antibiotics present.

Finally, even if a fungal medium is more sensitive for isolation of yeasts (Table 1), the overall level of detection of episodes that lead to revised therapy is not different in practice (Table 3). Moreover, the enhanced detection of bacteremia that should result from culturing the entire blood sample for bacteria may offset any patient benefit from the selective fungal medium. The general approach we favor is a system, such as the aerobic vented FAN bottle studied here, an aerobic resin medium as shown in other studies (5), or the LC system that also enables isolation of both bacteria and yeasts, albeit at a cost of increased labor and contamination, over a continuously monitoring automated system. Conclusions about the specific relative performance in practice of one medium versus another, however, can only be drawn based on clinical trials with adequate numbers of comparisons and control of all relevant variables, including the volume of blood cultured.

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