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Controlled Evaluation of the Agar-Slide and Radiometric Blood Culture Systems for the Detection of Bacteremia and Fungemia

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A commercially available agar-slide blood culture bottle (Septi-Chek; Roche Diagnostics, Div. Hoffman-La Roche, Inc., Nutley, N.J.) was compared with the radiometric blood culture system (BACTEC; Johnston Laboratories, Inc., Towson, Md.) in 8,544 paired blood cultures from adult patients. The systems were inoculated with equal volumes (10 ml) of blood. Overall, there was no statistically significant difference between the two systems in the recovery of clinically important microorganisms, but significantly more members of the family *Enterobacteriaceae* other than *Escherichia coli* were detected by the agar-slide system ($P < 0.005$). The agar-slide system detected more fungi, and the BACTEC detected more anaerobic bacteria; however, small numbers of recovered organisms precluded statistical significance. When microorganisms grew in both systems, their presence was detected one or more days earlier in the BACTEC ($P < 0.001$). More contaminants grew in the agar-slide system ($P < 0.001$). Both systems performed well, and either system should provide high yield and prompt detection of positive blood cultures in patients with bacteremia and fungemia if used in an optimal way as recommended by the respective manufacturers.

The agar-slide blood culture system (RSC; Septi-Chek; Roche Diagnostics, Div. Hoffmann-La Roche, Inc., Nutley, N.J.) and the radiometric blood culture system (BACTEC; Johnston Laboratories, Inc., Towson, Md.) are convenient and potentially time-saving variations of conventional broth blood culture methodology. Several recent evaluations of the RSC have demonstrated its abilities to detect more microorganisms causing sepsis and to detect them sooner than conventional broth systems (3, 4, 9, 18, 19). Similarly, there have been favorable evaluations of the BACTEC (2, 10, 13, 16). Our laboratories recently compared each of these systems with a conventional broth system that had been used as our standard (11, 19). In these evaluations the RSC and BACTEC each significantly outperformed the conventional system. Therefore, we directly compared the RSC and BACTEC in 8,554 cultures of equal volumes of blood at five collaborating hospitals.

MATERIALS AND METHODS

Collection of samples. During the study period, a 70-ml bottle of tryptic soy broth with 0.05% sodium polyanetholsulfonate (RSC; Roche) and two 30-ml BACTEC bottles (aerobic 6B and anaerobic 7D) of tryptic soy broth with 0.025% sodium polyanetholsulfonate were used for all blood cultures from adult patients at Middlesex General-University Hospital, the University of Colorado Hospital, the Denver Veterans Administration Medical Center, Vanderbilt University Medical Center, and the Salt Lake City Veterans Administration Medical Center. Patient blood cultures were obtained at the bedside after preparation of the skin with 10% povidone-iodine (1% available iodine) followed by 70% isopropyl alcohol. Blood from each separate venipuncture was distributed by needle and syringe as follows: 10 ml to the RSC bottle, 5 ml to the BACTEC 6B bottle, and 5 ml to the BACTEC 7D bottle. Thus, the volume of blood inoculated into both systems (10 ml) was the same (12), although the ratio of blood to broth was not the same (for RSC, 1:8; for Bactec 6B and 7D, 1:7).

Volume standards. To ensure that the culture bottles actually received the specified amounts of blood, we measured the level of fluid in each container after it was filled with blood. Although all blood-containing bottles were incubated, those with fluid levels below the standards were coded as inadequate and were excluded from subsequent analyses. Fluid level standards were set to ensure that at least 8 ml of blood was added to the RSC bottle and at least 4 ml each was added to the BACTEC 6B and 7D bottles.

Processing of samples. Identical methods were used for processing the blood cultures in the clinical microbiology laboratories at all five hospitals. All bottles were incubated in an air incubator at 35°C for 7 days. The RSC and BACTEC 6B bottles were examined macroscopically twice daily on days 1 and 2 of incubation and once daily thereafter through day 7. The BACTEC 7D bottle was examined macroscopically once daily.

On receipt of the samples in the laboratory, an agar-slide paddle was attached to the RSC bottle, and an immediate subculture was done by inverting the bottle and allowing the blood-broth mixture to cover the agar-coated paddle. A repeat subculture was done after 4 to 12 h of incubation and after each macroscopic examination if that examination was negative. If a bottle was positive macroscopically in the

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TABLE 1. Comparison of yield of clinically important bacteria and fungi from 10-ml samples of blood inoculated into tryptic soy broth processed in Septi-Chek and BACTEC (6B and 7D) blood culture bottles

Microorganism	No. of isolates recovered by:			P
	Both systems	BACTEC only	Septi-Chek only	
Aerobic and facultative bacteria	526	106	119	NS[a]
Gram positive	258	52	51	NS
Staphylococcus aureus	104	13	18	NS
Staphylococcus epidermidis	48	10	13	NS
Streptococcus pneumoniae	18	9	4	NS
Enterococci	35	9	7	NS
Viridans streptococci	25	3	4	NS
Other streptococci[b]	13	4	4	NS
Other[c]	14	2	1	NS
Gram negative	268	55	68	NS
E. coli	116	26	18	NS
Other members of the *Enterobacteriaceae*	97	16	40	<0.005
Pseudomonas aeruginosa	36	7	6	NS
Other[d]	19	6	4	NS
Anaerobic bacteria	6	14	5	NS
Gram positive[e]	2	3	0	NS
Gram negative[f]	4	11	5	NS
All bacteria	532	120	124	NS
Fungi[g]	35	4	13	NS

[a] NS, Not significant ($P > 0.05$).

[b] Includes the following numbers of isolates: group A streptococci, 10; group B streptococci, 6; nonenterococcal group D streptococci, 2; and group G streptococci, 3.

[c] Includes the following numbers of isolates: *Bacillus cereus*, 4; *Gardnerella vaginalis*, 1; group JK diphtheroids, 4; *Listeria monocytogenes*, 4; *Micrococcus* spp., 2; and *Nocardia asteroides*, 2.

[d] Includes the following numbers of isolates: *Acinetobacter* spp., 3; *Campylobacter intestinalis*, 1; *Haemophilus influenzae*, 7; *Neisseria gonorrhoeae*, 1; *Neisseria meningitidis*, 2; *Pseudomonas maltophilia*, 14; and an unidentified gram-negative rod.

[e] Includes the following numbers of isolates: *Clostridium perfringens*, 1; *Clostridium septicum*, 2; and *Peptococcus* sp., 2.

[f] Includes the following numbers of isolates: *Bacteroides fragilis*, 10; *Bacteroides* spp., 8; *Fusobacterium* sp., 1; and one unidentified anaerobic gram-negative rod.

[g] Includes the following numbers of isolates: *Candida albicans*, 37; *Candida parapsilosis*, 4; *Candida tropicalis*, 3; *Crytococcus neoformans*, 1; *Torulopsis glabrata*, 5; and 2 unidentified fungi.

broth but no growth was evident on the agar paddle, the slide chamber was removed, and a sterile Pasteur pipette was used to obtain broth for Gram stain and subcultures. If growth on the agar paddle was noted at the same time the broth became positive macroscopically, the initial mode of detection was considered to be the growth on agar, i.e., subculture.

BACTEC 6B bottles were shaken for the first 24 to 48 h of incubation, whereas BACTEC 7D and RSC bottles were not. After being examined visually, macroscopically negative BACTEC bottles were read radiometrically. BACTEC bottles with an increase of 10 or more growth index units between readings were examined by Gram stain and subcultured. In addition, 6B bottles with a growth index of 30 or greater and 7D bottles with a growth index of 20 or greater were examined by Gram stain and subcultured.

Clinical assessment. All patients with positive blood cultures were evaluated by an infectious-disease specialist who defined pathogens (clinically important microorganisms causing sepsis) and contaminants by established criteria (20). An episode of bacteremia or fungemia was defined by the first positive blood culture or by a new positive blood culture result occurring more than 2 days after the preceding positive (unless it was obvious clinically that the new positive did not represent a new bacteremic event). Any positive culture obtained within 48 h of a previous positive was considered to represent the same episode (20).

Analysis of data. Paired comparisons of the two blood culture systems were done only on adequately filled bottles that grew microorganisms causing true bacteremia and fungemia. Significance testing was done with the modified chi-square test described by McNemar (7).

RESULTS

A total of 8,554 adequately filled blood culture sets were received during the study period. Of these, 1,124 (13.1%) were positive, including 758 (8.9%) that grew microorganisms causing illness, 229 (2.7%) that grew contaminants, 8 (0.1%) that grew one or more contaminants and pathogens, and 129 (1.5%) that grew microorganisms that were indeterminate as a cause of sepsis. A total of 808 isolates associated with sepsis were detected; 547 isolates grew in both systems, and 255 of these were detected on the same day. A total of 684 (84.7%) isolates associated with sepsis grew in the RSC, whereas 671 (83.0%) grew in the BACTEC.

Overall, there was no statistically significant difference between the RSC and BACTEC in the recovery of clinically important bacteria and fungi (Table 1). However, members of the *Enterobacteriaceae* other than *Escherichia coli* were detected significantly more often in the RSC ($P < 0.005$). There was a trend favoring the RSC for the detection of fungi and a trend favoring the BACTEC for the detection of anaerobic bacteria. In each case, statistical significance would have been achieved had one more isolate been detected in the favored system.

When both systems detected sepsis, the BACTEC did so earlier. In 267 instances, the BACTEC was positive 1 or more days earlier than the RSC, whereas the converse occurred in 44 instances (Table 2). The speed advantage was present for all microorganism groups analyzed. The speed

TABLE 2. Comparison of speed of detection of clinically important bacteria and fungi grown from 10-ml samples of blood cultured in both Septi-Chek and BACTEC (6B and 7D) blood culture bottles

Microorganism	No. of isolates recovered by:			P
	Septi-Chek and BACTEC at same time	BACTEC ≥1 day earlier	Septi-Chek ≥1 day earlier	
Aerobic and facultative bacteria	240	244	41	<0.001
Gram positive	108	126	24	<0.001
Staphylococci	62	78	12	<0.001
Streptococci	42	41	8	<0.001
Other[a]	4	6	4	NS[b]
Gram negative	132	119	17	<0.001
Members of the *Enterobacteriaceae*	115	85	13	<0.001
P. aeruginosa	12	21	3	<0.001
Other[c]	5	13	1	<0.005
Anaerobic bacteria[d]	5	1	0	NS
Fungi	10	22	3	<0.001

[a] Includes the following numbers of isolates: *Bacillus cereus*, 3; group JK diphtheroids, 4; *L. monocytogenes*, 3; *Micrococcus* spp., 2; and *Nocardia asteroides*, 2.
[b] NS, Not significant ($P > 0.05$).
[c] Includes the following numbers of isolates: *H. influenzae*, 6; *P. maltophilia*, 11; and *Neisseria meningitidis*, 2.
[d] Includes the following numbers of isolates: *Clostridium septicum*, 2; *Bacteroides fragilis*, 3; and *Bacteroides* sp., 1.

advantage of the BACTEC was apparent, particularly after 1 and 2 days of incubation (Fig. 1). Mean detection times for BACTEC positives ranged from 1.1 days for pneumococci and *E. coli* to 2.6 days for fungi, whereas mean detection times for RSC positives ranged from 1.7 days for pneumococci to 3.7 days for fungi. In general, mean detection times with the BACTEC were 0.5 to 1 day earlier than with the RSC for similar microorganisms.

A total of 437 episodes of bacteremia and fungemia was detected during the study period, of which 321 were detected by both systems, 52 only by the BACTEC, and 64 only by the RSC ($P > 0.05$; not significant). There were 31 episodes (7.1%) of polymicrobial bacteremia. The RSC detected septicemia in 30 of these episodes, whereas the BACTEC detected sepsis in 27. The RSC failed to detect one of the microorganisms causing sepsis in eight episodes, two microorganisms in one episode, and three microorganisms in one episode. In only two of the 10 episodes in which microorganisms were missed by the RSC were the isolates obligate anaerobes. The BACTEC failed to detect one of the microorganisms causing sepsis in two episodes. The microorganisms not detected by each system in episodes of polymicrobial bacteremia and fungemia are listed in Table 3.

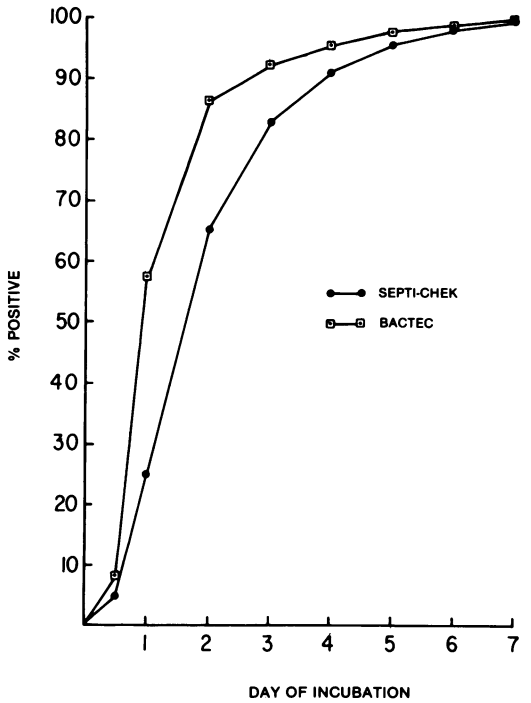

FIG. 1. Cumulative yields of positive blood cultures growing clinically important bacteria and fungi in Septi-Chek and BACTEC 460 blood culture systems.

Contaminant isolates occurred with greater frequency in the RSC than in the BACTEC (Table 4). In particular, *Staphylococcus epidermidis* ($P < 0.005$) and *Corynebacterium* species ($P < 0.005$) occurred more frequently in the RSC. Overall, 188 contaminant isolates occurred with the RSC, and 129 occurred with the BACTEC.

DISCUSSION

In this large, multicenter comparative evaluation, the Septi-Chek and BACTEC blood culture systems were equally effective overall in detecting bacteremia. Earlier, we had shown each system to be superior to the conventional broth blood culture system that had been our standard (11, 19). Consequently, these findings may be of particular interest to smaller laboratories in institutions that cannot afford the BACTEC instrumentation or to those who may have reservations about the use of the radiometric technology.

Although detection of microorganisms overall was equal in the two systems studied, the yield of members of the *Enterobacteriaceae* other than *E. coli* was significantly greater in the RSC. The explanation for this difference is not readily apparent. Detailed review of these isolates indicated that no single genus or species accounted for this finding. It is possible that the lower blood-to-broth ratio in the BACTEC bottles may have inhibited growth of some of these isolates (1, 12).

Trends favoring the BACTEC for the detection of anaerobic bacteria and the RSC for the detection of fungi were such that statistical significance almost was achieved. These findings might have been expected because of the methods used in this study. The RSC has been shown not to

TABLE 3. Microorganisms from polymicrobial bacteremia missed by Septi-Chek and BACTEC blood culture systems

Culture method	Microorganism(s) detected	Microorganism(s) missed
Septi-Chek	*E. coli*	*Bacteroides thetaiotaomicron*, *Bacteroides* sp.
	Staphylococcus aureus	*Klebsiella pneumoniae*
	Enterococcus	*E. coli*
	Enterobacter aerogenes	Enterococcus
	Staphylococcus epidermidis	*K. pneumoniae*
	Enterobacter cloacae	*Bacteroides fragilis*, *Bacteroides melaninogenicus*, *P. maltophilia*
	E. coli	*Serratia marcescens*
	P. aeruginosa, *Morganella morganii*	*E. cloacae*
	P. aeruginosa	Enterococcus
	Staphylococcus aureus, *E. coli*	Enterococcus
BACTEC	*P. aeruginosa*	*Candida albicans*
	P. aeruginosa	Enterococcus

be optimal for the detection of anaerobes (4, 18, 19), and the manufacturer recommends the use of a complementary unvented bottle for the detection of these microorganisms. Had such a bottle been used as part of the RSC, it is probable that the difference would not have been present. Since anaerobic environments inhibit and biphasic systems enhance the detection of fungi from blood (6, 15), the trend favoring the RSC for these organisms is explained easily. In this study 10 ml of blood was cultured in the aerobic RSC bottle versus 5 ml in the aerobic 6B bottle. Thus, half of the 10 ml of blood cultured in the BACTEC was in the anaerobic 7D bottle that would not be expected to grow fungi.

The speed advantage of the BACTEC was particularly impressive, since the RSC was significantly faster than the conventional broth system in our earlier evaluations (18, 19). Even when the time for subculture of the BACTEC bottles was taken into account, this system was significantly faster than the RSC in its ability to detect positive blood cultures. Two methodologic differences in the processing of the BACTEC and RSC might explain, at least in part, these differences. First, although all bottles were incubated in room air, the BACTEC bottles were back-flushed with CO_2 after each radiometric reading. The increased CO_2 in the BACTEC bottles may have promoted earlier growth of microorganisms. Also, agitation of the blood-broth mixture in the BACTEC 6B bottle during the early incubation period may have promoted earlier growth.

Although most clinicians would assume that the speed advantage of the BACTEC is significant clinically, there are few data to support this assumption. It is probable that the great majority of patients from whom blood cultures for presumed sepsis are obtained are on effective empirical antimicrobial therapy after (if not before) appropriate cultures have been obtained (17). Thus, it is unknown whether or not earlier culture results influence the outcome of bacteremia. On the other hand, earlier results that enable prompt direct antimicrobial susceptibility testing might allow more specific and less costly antimicrobial agents to be prescribed sooner (8, 17). In the present era of cost containment, such action could be beneficial.

A potential cause for concern with the RSC system as used in this study is its inability to detect all microorganisms in polymicrobial bacteremic episodes. This problem may have been largely methodologic, since a complementary anaerobic bottle for this system was not used as recommended (4, 18, 19). In only 2 of 10 episodes in which organisms were missed were the isolates obligate anaerobes. It may be that the relatively small surface area of the agar-coated paddle makes detection of different colony types more difficult when this system is used alone. However, we suspect that use of a complementary anaerobic bottle would have allowed detection of many of the facultatively anaerobic pathogens missed in this study.

Both blood culture systems used in this evaluation performed well, and each has advantages and disadvantages for potential users to consider. The major advantage of the BACTEC is its greater speed of detection of positive cultures, whereas its major disadvantage is its inability to accommodate larger volumes of blood (5, 14). Advantages of the Septi-Chek system include its ability to detect as many pathogens as, and possibly more than, the BACTEC and its ability to accommodate larger blood volumes than the

TABLE 4. Comparison of yield of contaminant microorganisms from 10-ml samples of blood inoculated into tryptic soy broth in Septi-Chek and BACTEC (6B and 7D) blood culture systems

Microorganism	No. of Isolates recovered by:			*P*
	Both systems	BACTEC only	Septi-Chek only	
Staphylococcus epidermidis	49	37	66	<0.005
Bacillus spp.	1	5	3	NS[a]
Corynebacterium spp.	6	3	28	<0.005
Propionibacterium spp.	1	5	10	NS
Other[b]	7	15	17	NS

[a] NS, Not significant ($P > 0.05$).

[b] Includes the following numbers of isolates: *Staphylococcus aureus*, 5; enterococci, 3; group G streptococci, 1; viridans streptococci, 11; *Lactobacillus* spp., 2; *Micrococcus* spp., 3; *E. coli*, 1; *K. pneumoniae*, 3; *Pseudomonas* spp., 2; *Acinetobacter* sp., 1; *Clostridium* spp., 2; *Peptococcus* spp., 2; *Bacteroides* sp., 1; *Megasphaera elsdenii*, 1; *Aspergillus* sp., 1; and one unidentified gram-negative rod.

BACTEC. Absence of capital costs for equipment and of radioactive material also may be seen as advantages by some potential users. The relatively high contamination rate and the need to use a conventional anaerobic bottle are disadvantages of this system. We conclude that either of the systems studied will provide high yield and prompt detection of positive blood cultures in bacteremic patients if used in an optimal way as recommended by the respective manufacturers.

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