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Controlled Clinical Comparison of Two Lysis-Based Blood Culture Systems, Isolator and Septi-Chek Release, for Detection of Bloodstream Infections

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A controlled clinical comparison was made of the Isolator (Wampole Laboratories, Cranbury, N.J.) and the Septi-Chek Release bottle (Roche Diagnostics, Nutley, N.J.). From 6,345 blood culture sets fulfilling minimum criteria for volume of blood cultured, 840 strains were isolated, of which only 691 (82%) were considered to be representative of bloodstream infection according to Centers for Disease Control definitions. Statistically significant differences were found between the systems for the following organisms, which were all detected more frequently in the Isolator system: Staphylococcus aureus (P = 0.0001), Alcaligenes xylosoxidans (P = 0.008), Klebsiella pneumoniae (P = 0.05), Salmonella spp. (P = 0.03), and Candida albicans (P = 0.02). The Septi-Chek Release system required a longer period of time than the Isolator system for detection of the following organisms: S. aureus (P = 0.0001), Enterococcus spp. (P = 0.0001), Enterobacter cloacae (P = 0.03), Escherichia coli (P = 0.0001), Klebsiella oxytoca (P = 0.03), K. pneumoniae (P = 0.02), Pseudomonas aeruginosa (P = 0.002), and C. albicans (P = 0.005). There were 430 episodes of bloodstream infections identified in the study; of these episodes, only those due to S. aureus were detected significantly more frequently (P = 0.0001) by the Isolator system than by the Septi-Chek Release system. However, episodes of bloodstream infections due to S. aureus, Staphylococcus epidermidis, Enterococcus spp., and E. coli were detected significantly faster by the Isolator system.

Although a lysis-centrifugation system (Isolator; Wampole Laboratories, Cranbury, N.J.) has been commercially available for several years for the recovery of bacteria, mycobacteria, and fungi from blood, the development and evaluation of a lysis-broth system (Septi-Chek Release culture bottle; formerly Roche Diagnostic Systems, Nutley, N.J., and currently Becton Dickinson and Company, Hunt Valley, Md.) has occurred only recently (3, 4). Moreover, only a limited comparison has been made between the Isolator and Release systems, which provided inconclusive results because of the small sample size of the study and the small number of positive cultures (3). Both systems contain saponin as the principal lytic agent but differ in that any microorganisms present in the blood sample are subcultured onto saponin-free (and antimicrobial agent-free) media with the Isolator sediment, whereas microorganisms remain exposed to saponin (and antimicrobial agents) in the blood-broth mixture. The purpose of this study was to carry out a controlled clinical evaluation of the Isolator and Release systems.

MATERIALS AND METHODS

Blood was obtained by phlebotomists from adult patients with clinically suspected sepsis and inoculated aseptically at the patient’s bedside into an Isolator tube and a Septi-Chek Release bottle containing brain heart infusion broth and saponin. Blood samples were divided equally between the systems. During the first half of the study, the Isolator tube was inoculated first; this sequence was reversed during the second half of the study. Only blood culture sets containing at least 6 ml of blood in each system were included in the study.

The Isolator sediment was inoculated onto blood agar and chocolate agar which were incubated for a minimum of 72 h at 35°C in an atmosphere of air enhanced with 5 to 10% CO2 and onto brain heart infusion agar with 5% sheep blood and potato dextrose agar which were incubated for 7 days at 30°C in an atmosphere of room air. No anaerobic cultures of the Isolator sediment were performed.

Upon its receipt in the laboratory, the Septi-Chek slide was attached to the Release bottle in a biological safety cabinet, and the bottle was tilted to allow the blood-broth mixture to flow into the slide chamber. Bottles were then incubated at 35°C on a rotary shaker (150 rpm) for the first 18 to 24 h and then in a stationary state for a total of 5 days.

For blood cultures received by 10 a.m. on a particular day, the first examination for visible evidence of growth on all plates and in all bottles took place at approximately 4 p.m. the same day. All plates and bottles were reexamined daily thereafter.

Isolates from positive cultures were identified by standard methods, and their clinical significance was assessed according to definitions for bloodstream infections published by the Centers for Disease Control (CDC) (1). The two blood cultures systems were then compared statistically on the basis of the numbers of clinically significant isolates and septic episodes detected. A new septic episode was defined as the initial isolation of a clinically significant organism, the subsequent isolation of a different clinically significant organism, or the isolation of the same organism after at least a 5-day interval since the previous positive culture with this organism.

Statistical analysis of the results was carried out by methods described by Ilstrup (2).
TABLE 1. Positive cultures by system

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. positive</th>
<th>No. of positives detected by:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolator only</td>
<td>Release only</td>
<td>Both systems</td>
</tr>
<tr>
<td>Alcaligenes xylosoxidans</td>
<td>12</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>17</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>49</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>10</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Klebsiella pneumoniae</td>
<td>28</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>7</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Serratia marcescens</td>
<td>16</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>31</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Xanthomonas maltophilia</td>
<td>12</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>55</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Streptococcus spp., viridans group</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>185</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>87</td>
<td>26</td>
<td>29</td>
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<tr>
<td>Staphylococcus spp., coagulase negative*</td>
<td>40</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>36</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Torulopsis glabrata</td>
<td>15</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

* Species other than S. epidermidis.

RESULTS AND DISCUSSION

A total of 6,345 blood culture sets were received during the study. A total of 840 isolates were recovered; however, only 691 (82%) were identified as being associated with bloodstream infections according to CDC definitions (1). Among species representative of bloodstream infections and present in sufficient numbers for statistical analysis (Table 1), the Isolator system detected the following species significantly more frequently: Alcaligenes xylosoxidans (P = 0.008), Klebsiella pneumoniae (P = 0.05), Salmonella spp. (P = 0.03), Staphylococcus aureus (P = 0.0001), and Candida albicans (P = 0.02).

There were a number of species that represented bloodstream infections but that occurred in numbers so small as to preclude statistical analysis. Among these were 15 isolates detected by Isolator only (Acinetobacter anitratus, 3; CDC group IV-2, 1; Enterobacter spp., 2; Gemella spp., 1; Neisseria subflava, 1; Staphylococcus spp., 1; Stomatococcus spp., 1; Aspergillus flavidus, 1; Candida humicola, 1; Fusarium spp., 1; Rhodotorula rubrum, 1; and Streptomyces spp., 1), 14 isolates detected by the Septi-Chek Release only (anaerobic non-spore forming gram-positive bacillus, 1; Bacteroides fragilis group, 4; Clostridium ramosum, 1; Propionibacterium acnes, 1; Corynebacterium spp., 3; Morganella morganii, 1; Moraxella osloensis, 1; Aspergillus fumigatus, 1; and Candida krusei, 1), and 23 isolates detected by both systems (Aerococcus spp., 3; Bacillus spp., 2; Corynebacterium jeikeium, 1; Lactobacillus spp., 1; Proteus mirabilis, 2; Pseudomonas cepacia, 2; Serratia liquefaciens, 2; Streptococcus group A, 2; Streptococcus group B, 5; Streptococcus pneumoniae, 3; Streptococcus spp., 1; and Candida tropicalis, 1).

The mean and median times for detection of organisms associated with bloodstream infections are shown in Table 2. Paired Wilcoxon signed-rank tests showed that the Septi-Chek Release bottle required a longer period for detection of growth than the Isolator system for the following organisms: S. aureus (P = 0.0001), Staphylococcus epidermidis (P = 0.0001), Enterococcus spp. (P = 0.0001), Enterobacter cloacae (P = 0.03), Escherichia coli (P = 0.0001), Klebsiella oxytoca (P = 0.03), K. pneumoniae (P = 0.02), Pseudomonas aeruginosa (P = 0.002), and C. albicans (P = 0.005). Two factors probably contributed to this difference: (i) the hemolysis and turbidity of the blood-broth mixture in the Release bottle, regardless of whether growth was present, and (ii) the filmlike appearance of growth on the agar slant in the Septi-Chek attachment.

There were 430 episodes of bloodstream infections (septic episodes) in 252 patients identified during the study (Table 3). A difference between systems in detecting episodes of bloodstream infections was limited to episodes of S. aureus bacteremia which were detected significantly more frequently by the Isolator system (P = 0.0001); however, the detection of septic episodes was significantly longer in the Septi-Chek Release system than in the Isolator system for those due to S. aureus (P = 0.0001), S. epidermidis (P = 0.0002), Enterococcus spp. (P = 0.0005), and E. coli (P = 0.001).

In the comparison by Murray et al. (3) of the recovery of pathogens with Septi-Chek brain heart infusion broth with saponin (i.e., the Release system), Septi-Chek tryptic soy broth, and Isolator, inoculation of the Isolator was limited to blood cultures from patients with suspected fungemia. As a result, only 1,776 specimens were inoculated into both the Septi-Chek Release bottle and Isolator system. Excluding presumed contaminants, there were 130 isolates. The authors commented that the overall yield from the Septi-Chek Release system was significantly greater than that from Isolator; however, the number of individual species and/or genera which were isolated in sufficient numbers for statistical analysis was obviously small. Murray et al. (3) observed a higher rate of recovery of isolates (10 of 13) of coagulase-negative staphylococci from the Release system than from the Isolator. The exact cause of this difference is unclear but
may be related to different criteria for defining "pathogens," since Murray et al. (3) did not use CDC definitions for bloodstream infections and excluded only single isolates of coagulase-negative staphylococci from their analysis. Of special interest in their study was the equivalent recovery of Candida spp. from both systems (Isolator only, 8; Release only, 10; and both, 7) and the higher recovery of Torulopsis glabrata from the Septi-Chek Release system (Isolator only, 1; Release only, 7; and both, 7). We did not observe this difference with T. glabrata. Also, contrary to observations by Murray et al. (3), we observed no statistically significant difference in the recovery of P. aeruginosa between systems with a larger number of isolates.

Both Murray et al. (3) and Rohner et al. (4) found the Septi-Chek Release system with brain heart infusion broth containing saponin to provide increased yields of bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Isolator</th>
<th>Release</th>
<th>Differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of isolates detected</td>
<td>No. of days to detection</td>
<td>No. of isolates detected</td>
</tr>
<tr>
<td>Alcaligenes xylosoxidans</td>
<td>12</td>
<td>3.6</td>
<td>3.0</td>
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<tr>
<td>Citrobacter freundii</td>
<td>7</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>15</td>
<td>1.4</td>
<td>1.0</td>
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<tr>
<td>Escherichia coli</td>
<td>41</td>
<td>1.4</td>
<td>1.0</td>
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<td>Klebsiella oxytoca</td>
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<td>Yersinia enterocolitica</td>
<td>2</td>
<td>2.0</td>
<td>2.0</td>
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<td>Pseudomonas aeruginosa</td>
<td>27</td>
<td>1.6</td>
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<td>Xanthomonas malophilia</td>
<td>11</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>49</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Streptococcus spp., viridans group</td>
<td>8</td>
<td>1.9</td>
<td>2.0</td>
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<tr>
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<td>2.0</td>
</tr>
<tr>
<td>Staphylococcus spp., coagulate negativeb</td>
<td>16</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>32</td>
<td>2.2</td>
<td>2.0</td>
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<tr>
<td>Candida parapsilosis</td>
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<td>3.3</td>
<td>3.0</td>
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<tr>
<td>Cryptococcus neoformans</td>
<td>6</td>
<td>2.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Torulopsis glabrata</td>
<td>12</td>
<td>2.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

a Mean and median difference (in days) when detected by both systems. No., number of isolates detected by both systems. b Species other than S. epidermidis.

TABLE 3. Number of bloodstream infections detected by system

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total no. detected</th>
<th>No. of infections detected by:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolator only</td>
<td>Release only</td>
<td>Both systems</td>
</tr>
<tr>
<td>Alcaligenes xylosoxidans</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
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<tr>
<td>Enterobacter aerogenes</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>15</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>37</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>20</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Salmonella spp.</td>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>10</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Yersinia enterocolitica</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>23</td>
<td>8</td>
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<tr>
<td>Xanthomonas malophilia</td>
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<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
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<tr>
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<td>5</td>
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<td>Staphylococcus aureus</td>
<td>101</td>
<td>52</td>
<td>13</td>
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<tr>
<td>Staphylococcus epidermidis</td>
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<td>23</td>
<td>27</td>
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<td>Staphylococcus spp., coagulate negativea</td>
<td>37</td>
<td>11</td>
<td>23</td>
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<tr>
<td>Candida albicans</td>
<td>22</td>
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<tr>
<td>Candida parapsilosis</td>
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<td>1</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Torulopsis glabrata</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

a Species other than S. epidermidis.
and yeasts compared with those obtained with broth media unsupplemented with saponin. In the study by Murray et al. (3) the comparison system was a Septi-Chek bottle containing tryptic soy broth, whereas in the study by Rohner et al. (4) the comparison system was a Septi-Chek bottle containing brain heart infusion broth. Both of these studies included paired comparisons of non-lysis- and lysis-based broth systems for blood cultures of all patients suspected of having septicemia. As already mentioned, Murray et al. (3) compared the lysis-based broth system with the Isolator system on a small selected subset population of patients, so the discrepancies between their findings and ours may reflect differences between the populations and numbers of patients studied. Whether differences between the two systems in concentrations of or exposure times to saponin could account for the differences in recovery of microorganisms that we observed in our study remains open to speculation. Although several species of microorganisms, including S. aureus, were detected significantly more frequently in the Isolator system, significantly increased frequency of detection of septic episodes in the Isolator system was limited to those associated with S. aureus. In most instances, such episodes were associated with the presence of only one or two CFUs on a single agar medium inoculated with Isolator sediment, thereby representing on average 0.2 CFU/ml.

In conclusion, although blood culture systems using saponin-supplemented biphasic media appear to provide improved recovery of isolates of many organism groups compared with biphasic blood culture media not supplemented with saponin (3, 4), it did not appear that the Septi-Chek Release system was equivalent to the other commercially available lysis-based system, the Isolator, as regards the detection of isolates associated with bloodstream infections or episodes of bloodstream infections.

ACKNOWLEDGMENTS

This study was supported in part by Roche Diagnostics and by a grant from Becton Dickinson and Company.

REFERENCES