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Effect of Delay in Processing on Lysis-Centrifugation Blood Culture Results from Marrow Transplant Patients

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The effect of delay in processing on results of lysis-centrifugation (LC; Isolator) blood cultures was assessed in 4,577 paired blood specimens. Blood specimens were obtained at all hours from 384 febrile marrow transplant patients with indwelling venous catheters and were processed by the LC technique and by a conventional two-bottle method. Most patients (84%) were receiving broad-spectrum antibiotics at the time of blood culture. Specimens were delivered to the laboratory, where Isolator tubes were held at 35°C and processed in batches between 0700 and 1730 h daily. This procedure resulted in a delay beyond the manufacturer-suggested processing time of less than 8 h for 1,853 (42%) of the LC cultures. There was no overall difference in the recovery of organisms present in LC cultures processed after being held for 8 to 24 h compared with the conventional two-bottle method. LC methodology had shorter time to detection than the conventional method for detection of *Candida* spp. and *Pseudomonas* spp. ($P < 0.05$). However, time to detection for *Streptococcus* spp. and members of the family *Enterobacteriaceae*, responsible for 16.3% of total isolates, was prolonged significantly by delay in processing when compared with the conventional two-bottle method ($P < 0.01$). Results of this study support the recommendation of the manufacturer for processing of Isolator tubes within 8 h or less. Although one can safely delay processing beyond 8 h in terms of total recovery of organisms, such delays were associated with longer time to detection for certain important potentially pathogenic organisms which accounted for a sizeable proportion of blood culture isolates from marrow transplant patients.

Rapid, accurate detection of organisms causing bacteremia or fungemia occupies a central role in the clinical microbiology laboratory supporting marrow transplant and other immunocompromised patients. Profound granulocytopenia is experienced by all marrow transplant patients and is associated with a high incidence of bacterial and fungal infection (22). Virtually all marrow transplant patients receive systemic broad-spectrum antibiotics throughout the period of granulocytopenia until marrow engraftment, and sustained peripheral granulocyte counts of greater than 500 cells per mm^3 are achieved (25). Thus, blood culture techniques which are better able to detect organisms rapidly in the presence of antibiotics would be beneficial in this setting.

The lysis-centrifugation (LC) (Isolator; E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.) technique has been studied extensively (1, 3, 4, 9, 11, 12, 16–19, 29), and several authors report that LC may be advantageous for detecting organisms in the presence of antibiotics (12, 16, 23, 29). The LC technique, however, requires centrifugation and manipulation, which cannot always be promptly performed in laboratories with limited staffing. The manufacturer recommends that Isolator tubes be processed in less than 8 h after collection. A previous study found a significantly higher yield from Isolator tubes stored at room temperature and processed within 9 h than from tubes with a greater than 9-h-delay time and recommended that tubes be processed within 9 h of collection (28). That study did not include comparison with paired culture results in which there was no delay (28). Interestingly, this same study noted that not all species exhibited a decline in frequency of recovery as processing of the tubes was delayed. In fact, *Enterobacter* spp., *Escherichia coli*, *Staphylococcus aureus*, and the viridans group streptococci demonstrated minor increases in frequency of recovery for the delay period greater than 9 h (28). An earlier in vitro study demonstrated that low numbers of organisms could survive in Isolator tubes held at 22 and 34°C for 15 h and that the number of detectable organisms actually increased during this period in 55 of 91 and 72 of 91 strains, respectively (7). Thus, it is not clear that extended delay in processing necessarily results in loss of viable organisms and diminished frequency of recovery.

The present study was designed as a paired trial to compare results using 10-ml Isolator tubes held at 35°C with results using a 10-ml blood volume cultured by the conventional two-bottle method for simultaneous recovery of bacteria and fungi in specimens from marrow transplant patients receiving antibiotics.

MATERIALS AND METHODS

Blood collection and handling. All blood specimens were obtained from patients admitted to the Fred Hutchinson Cancer Research Center for marrow transplantation between 1 June 1984 and 1 May 1986. Blood collection and handling has been previously described (9). Briefly, 20-ml of blood was drawn into a sterile syringe by nursing personnel from the indwelling Hickman right atrial catheter (13) or from a peripheral vein of the patient. The blood specimen was then divided at the bedside as follows: 5 ml each was injected aseptically into bottles containing (i) 45 ml of peptone II broth (Becton Dickinson Vacutainer Systems, Rutherford, N.J.) and (ii) glucose phosphate broth and GC agar slant (PML Microbiologicals, Tualatin, Oreg.); the remaining 10 ml was injected into a 10-ml Isolator tube. The culture bottles and Isolator tube were then labeled at the

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bedside and delivered to the microbiology laboratory and placed in the 35°C incubator.

Processing of conventional biphasic and broth bottles. Both bottles were held in an upright position at 35°C for 7 days and examined twice daily for growth. Bottles were inverted, mixed, and allowed to settle, thus, the biphasic bottle contents were, in effect, subcultured with each examination.

Processing of Isolator tubes. Isolator tubes were incubated at 35°C before batch centrifugation during the 0700 to 1730 operating hours of the laboratory. Isostat processing of tubes was performed in a vertical laminar air-flow hood (9). Sediment portions were inoculated onto (i) aerobic medium consisting of enriched chocolate agar, sheep blood agar, and inhibitory Candida BCG agar and (ii) anaerobic medium consisting of sheep blood agar. Plates were examined twice daily in a manner similar to the examination of blood culture bottles.

Detection of positive blood specimens. Positive specimens were defined by growth in either bottle or by colonies appearing within the inoculum-streaked area of an Isolator plate. Appropriate smears and stains were made, and subcultures were made aerobically and anaerobically according to the appearance of organisms, after interpretation of the Gram stain of smears from each positive bottle or plate (26). Organisms were identified by standard laboratory methods as described in relevant chapters of the *Manual of Clinical Microbiology* (20). The CFU were recorded for each plate and quantitation (CFU per milliliter) of organisms detected by LC was calculated by a method previously described (10).

Definitions. The time between drawing blood from the patient and the time the Isolator sediment was inoculated onto individual plates was defined as the delay-in-processing time. The time to detection was defined as the total time in hours elapsed between the time of drawing blood from the patient and the time a positive culture was noted. Antimicrobial agents present at the time of sampling were documented by review of the medical records of each patient.

Statistical analysis. Only blood specimens submitted in properly filled combinations of Isolator tube, biphasic bottle, and peptone bottle were evaluated in this study. For purposes of analysis, results of the aerobic biphasic bottle and the anaerobic peptone bottle were combined as the conventional method. Organisms were grouped into six categories,

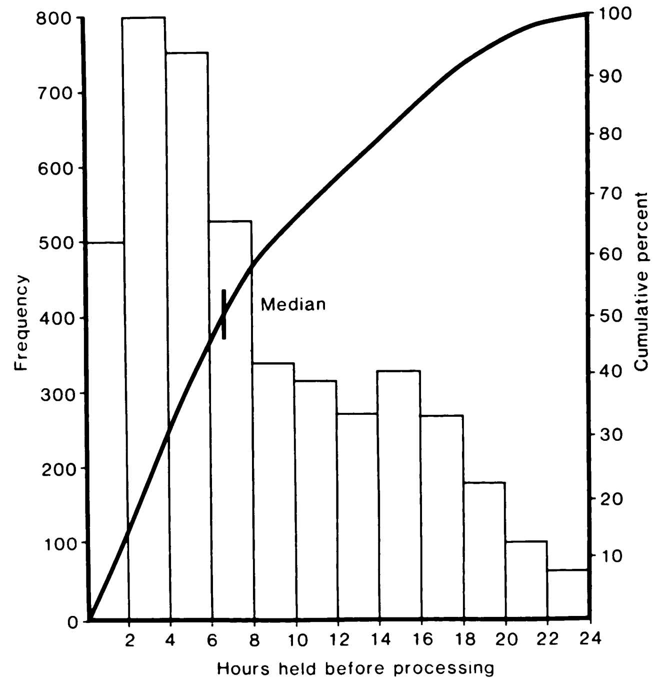

FIG. 1. Distribution of all cultures by time of delay in processing associated with 10-ml Isolator tubes (in 2-h increments).

Staphylococcus spp., *Streptococcus* spp., members of the family *Enterobacteriaceae*, *Pseudomonas* spp., *Candida* spp., and others, for statistical analysis. The effect of delay in processing associated with the LC method was examined by using analysis of variance to compare the results of three categories as follows: (i) positive by LC but not by conventional method, (ii) positive by conventional method but not by LC, and (iii) positive by both methods (27). A proportional hazards regression (Cox) model was used to analyze differences in time to detection between the two methods (15). Variables in the model included patient, culture method, delay-in-processing time associated with LC, pairs, time to detection, CFU per milliliter, and organism group.

TABLE 1. Comparison of organisms recovered by LC and conventional (C) methods when examined by organism group and delay in processing beyond the manufacturer recommendation for LC

Organism (no.)	No. of organisms recovered when processed within 8 h (2,573 specimens) by:		No. of organisms recovered when processed after 8 h (1,853 specimens) by:	
	LC	C	LC	C
Staphylococcus spp. (242)[a]	80	69	48	45
Streptococcus spp. (41)[b]	12	12	9	8
Members of the *Enterobacteriaceae* (68)[c]	19	24	12	13
Pseudomonas spp. (61)[d]	24	15	12	10
Candida spp. (164)[e]	55	50	33	26
Other (91)[f]	36	17	24	14
Total (667)[g]	226 (8.7%)	187 (7.2%)	138 (7.2%)	116 (6.3%)

[a] Includes 29 *Staphylococcus aureus*, 2 *S. hominis*, 2 *S. saprophyticus*, and 209 coagulase-negative species not further identified.
[b] Includes 3 *Streptococcus pneumoniae*, 29 viridans group streptococci, and 9 *Enterococcus* spp.
[c] Includes 6 *Citrobacter freundii*, 26 *Escherichia coli*, 23 *Enterobacter* spp., 11 *Klebsiella pneumoniae*, and 2 *Serratia marcescens*.
[d] Includes 38 *Pseudomonas aeruginosa*, 20 *P.(Xanthomonas) maltophilia*, and 3 *Pseudomonas* spp.
[e] Includes 108 *C. albicans*, 4 *C. glabrata*, 4 *C. krusei*, 27 *C. parapsilosis*, and 21 *C. tropicalis*.
[f] Includes 17 *Acinetobacter* spp., 1 *Aerococcus* sp., 1 *Agrobacterium radiobacter*, 3 *Aspergillus* spp., 1 *Aureobasidium pullulans*, 4 *Bacillus* spp., 6 *Bacteroides* spp., 3 *Capnocytophaga* spp., 9 *Corynebacterium* spp., 2 *Cryptococcus* spp., 1 *Epicoccum* sp., 1 *Hyalodendron* sp., 16 *Micrococcus* spp., 3 *Moraxella* spp., 1 atypical *Mycobacterium* sp., 1 *Oedocephalum* sp., 3 *Propionibacterium* spp., 7 *Rhodococcus equi*, 3 *Rhodotorula* spp., 2 *Rothia* sp., 4 *Streptomyces* spp., 1 *Torulopsis candida*, and 1 yeastlike isolate which could not be identified due to lack of characteristic morphology and sugar assimilation pattern.
[g] $P > 0.05$ for LC method; $P > 0.05$ for conventional method.

TABLE 2. Comparison of detection of organisms within paired samples for the conventional method (C), which had no delay, and the LC method, which had an associated time of delay in processing, and total pairs processed

Delay in h	No. of organisms recovered by: LC (n = 364)	Paired C (n = 303)	Total pairs processed (n = 4,426)
2	42	34	500
<4	85	66	797
<6	51	45	750
<8	49	42	526
<10	28	27	338
<12	15	13	313
<14	13	12	271
<16	25	23	326
<18	22	15	267
<20	15	13	178
<22	7	7	98
<24	12	6	62

RESULTS

Organisms were detected in 586 (12.8%) of 4,577 paired specimens from 149 (38.8%) of 384 patients. A total of 153 organisms from 151 (3.3%) specimens were determined to be contaminants by study criteria. These results have been discussed elsewhere (9) and are not included in this analysis. The 469 isolates from 435 (9.5%) of the remaining 4,426 specimens were deemed clinically significant by the same criteria and were examined for the effect of delay in processing on frequency of detection and time to detection. There were 394 (84%) organisms detected in the presence of one or more broad-spectrum antibiotics. Overall, significantly more organisms were detected by the LC method than by the conventional method (364 of 469 [77.6%] versus 303 of 469 [64.6%]; $P < 0.001$).

The delay in processing for the Isolator tubes ranged from less than 1 to 24 h, and the median time of processing was 6.7 h (Fig. 1). A total of 1,853 (42%) cultures were processed beyond the manufacturer-suggested guideline of less than 8 h. Distribution of recovered organisms is displayed in Table 1. No *Neisseria* spp. or *Haemophilus* spp. were detected in the study. Two *Streptococcus pneumoniae* isolates were detected by LC, while only one of the two was detected by the conventional method. Thirty-one (7.1%) specimens yielded two or more organisms. Coagulase-negative staphylococci accounted for 32% of the total isolates recovered. Frequency of detection by each method, compared with LC delay in processing, is shown in Table 2. Although the rate of recovery for all organisms was higher for specimens processed in less than 8 h than the rate of recovery for specimens processed at greater than 8 h (8.8 versus 7.2%), this difference was not statistically significant for total recovery, any individual organism, or any organism group. Comparison of means for the delay-in-processing time of each category of positive isolates by analysis of variance detected no significant differences within any of the organism groups ($P > 0.3$) (Table 3).

The number of organisms (CFU per milliliter) detected ranged from 0.1 CFU/ml to greater than 10^6 CFU/ml. Of the 364 organisms detected by LC, 62% were present in concentrations of less than 1 CFU/ml. Isolates from LC cultures with delay in processing beyond the 8-h recommendation of the manufacturer were no more likely to be detected at concentrations less than or greater than 1 CFU/ml, with the exception of *Pseudomonas* spp. Of the 36 *Pseudomonas* spp. recovered, 12 isolates were found in specimens held for greater than 8 h and 10 (83%) of these contained greater than 1 CFU/ml compared with 9 (37.5%) of 24 isolates detected in specimens processed within less than 8 h ($P < 0.01$).

Comparison between the antibiotic susceptibility pattern for the organism detected and the antibiotic treatment of the patient at the time of culture revealed that 232 (63.7%) of 364 organisms were detected in the presence of potentially effective parenteral antibiotics. Most were found in concentrations of less than 1 CFU/ml (Table 4). However, 132 (36.3%) organisms detected in the absence of effective parenteral antibiotics (including those detected in the absence of any antibiotics) were no more likely to be found in concentrations of less than 1 CFU/ml than those with greater than 1 CFU/ml (Table 4). If we assume that isolates detected only by the conventional method contained less than 1 CFU/ml, isolates detected by the conventional method had a proportionally similar distribution.

Positive blood specimens with higher concentrations (CFU per milliliter) of organisms consistently had shorter times to detection by either method when examined by the proportional hazards regression model ($P < 0.00001$) (Table 5). When the model was corrected for concentration of organisms, the LC method detected *Pseudomonas* spp., *Candida* spp., and the group of other organisms faster than the conventional method ($P < 0.05$, $P < 0.001$, and $P < 0.05$, respectively). *Streptococcus* spp. and members of the family *Enterobacteriaceae* were detected more rapidly by the conventional method ($P < 0.01$). *Staphylococcus* spp. were detected faster by LC than by the conventional method, but this difference was not statistically significant. Figure 2

TABLE 3. Comparison of mean hours of delay in processing for 667 positive specimens

Organism (no. of sample pairs)	Mean h of delay in processing (SE) by: LC only	Conventional only	Both methods
Staphylococcus spp. (242)	8.42 (7.39)	9.05 (6.08)	8.59 (6.55)
Streptococcus spp. (41)	10.25 (6.97)	9.89 (7.44)	7.63 (6.10)
Members of the *Enterobacteriaceae* (68)	13.00 (7.07)	7.03 (5.56)	8.27 (6.40)
Pseudomonas spp. (61)	6.28 (5.40)	7.25 (2.87)	7.16 (5.55)
Candida spp. (164)	8.14 (5.12)	7.86 (5.39)	7.42 (5.60)
Other (91)[a]	9.42 (7.64)	9.35 (7.01)	7.93 (4.93)

[a] All other organisms which individually had less than 20 total positive isolates.

TABLE 4. Effect of antibiotics on the recovery of 364 organisms isolated from LC blood cultures processed in less than 8 h and those held for greater than 8 h

Parenteral antibiotic treatment	No. of organisms: Delay in processing (< or = 8 h) organism (CFU/ml) <1	>1	Delay in processing (>8 h) organism (CFU/ml) <1	>1
Effective	101[a]	42	57[b]	32
Not effective[c]	44	40	25	23
Total	145	82	82	55

[a,b] Not significant, $P > 0.1$.
[c] Includes no antibiotics.

TABLE 5. Comparison of concentrations (CFU/ml) of organisms and mean hours to detection for 667 positive specimens

Organism (no. of sample pairs)	h to detection (no. of isolates) by LC (CFU/ml)		h to detection (no. of isolates) by conventional method (CFU/ml)	
	<1	>1	<1	>1
Staphylococcus spp. (242)	57.0 (81)	32.5 (46)	50.3 (75)	44.0 (40)
Streptococcus spp. (41)	71.1 (11)	38.2 (10)	41.5 (11)	23.0 (9)
Members of the *Enterobacteriaceae* (68)	34.3 (8)	23.6 (23)	31.6 (16)	20.2 (21)
Pseudomonas spp. (61)	45.4 (7)	32.2 (19)	57.0 (11)	33.9 (14)
Candida spp. (164)	58.2 (62)	47.9 (27)	69.6 (51)	71.0 (24)
Other (91)[a]	99.1 (48)	54.9 (12)	83.5 (26)	26.9 (5)

[a] All other organisms which individually had less than 20 total positive isolates.

compares the detection of positive isolates versus time to detection for the two methods for *Pseudomonas* spp., *Candida* spp., *Streptococcus* spp., and members of the *Enterobacteriaceae*. When correction was made in the model for delay in processing as well as CFU per milliliter, the two methods did not differ significantly for time to detection of members of the *Enterobacteriaceae* or *Streptococcus* spp., indicating a direct relationship between delay in processing and time to detection for these organisms. As expected, time to detection remained significantly different in this corrected model for all other groups of organisms, with detection faster by the LC method than by the conventional method when corrected for CFU per milliliter ($P < 0.01$).

DISCUSSION

We have previously reported that LC is a useful addition to blood culturing methodology for marrow transplant patients who are receiving antibiotics at the time of culture (9). Most prior studies have focused on the efficacy of the Isolator when handled according to the guideline of the manufacturer for processing within 8 h (3, 4, 11, 16, 19, 29). These studies generally reported the holding of LC tubes at room temperature before processing within the manufacturer-recommended guideline of 8 h, although one study reports refrigeration of tubes up to 4 h before centrifugation and processing (12). However, several investigators have reported results found with overnight delay in processing for Isolator tubes held at room temperature (1, 17, 18). The potential effect of this delay on results was not specifically addressed in these studies. Likewise, studies of the 1.5-ml pediatric Isolator tubes, processed by direct inoculation onto solid agar plates, have also reported delays beyond 8 h (5, 6, 30). These lysis-direct plating studies also did not examine the effect of delay in processing on results. However, for each study in which a delay occurred beyond 8 h, investigators report equivalent or better recovery of organisms, including the recovery of *Streptococcus pneumoniae*, with Isolator tubes (1, 5, 6, 17, 18, 30).

Isenberg (14) seeded 77 different microbial species onto blood samples at concentrations approximating 1 or 10 CFU/ml and processed the simulated cultures by LC. Despite processing within 30 min, he found that organisms were generally recovered in numbers 11 to 98% below those recovered from phosphate-buffered saline (14). One reason for loss of viability might be the toxic properties of whole blood, properties which form the rationale for the use of broth dilution in blood culturing (26). A previous clinical study reported a significantly higher yield from Isolator tubes stores at room temperature and processed within 9 h than from those processed after 9 h, 8.8 versus 7.3%, respectively ($P < 0.05$), and appears to document loss of viability due to delay in processing (28). However, that study

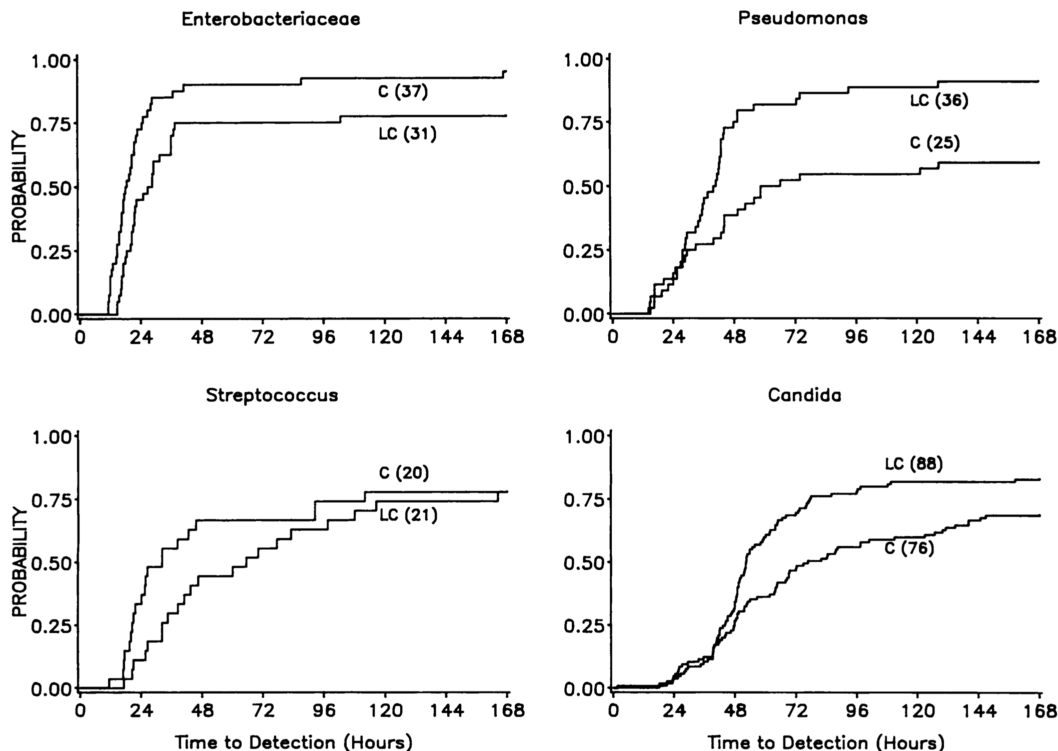

FIG. 2. Comparison of detection probability versus time to detection in hours for the LC and conventional (C) methods.

did not compare recovery from paired cultures not subject to delay.

If we examine our data using the methods employed by these investigators, we can demonstrate, similarly, that Isolator tubes processed before 8 h yield a higher rate of detection than those processed after 8 h, 8.7 versus 7.2%; this difference is not statistically significant ($P > 0.05$). This result is almost identical to that previously reported using room temperature incubation (28). Similarly, if we examine the paired blood samples processed by the conventional method, we also find a higher yield for those samples paired with Isolator tubes processed in less than 8 h than for those paired with Isolator tubes processed after a greater-than-8-h delay, 7.2 versus 6.3%; this difference is also not statistically significant ($P > 0.05$). Thus, the apparent decreased yield from tubes held beyond 8 h quite possibly could be caused by an artifact of Poisson distribution for the entire sample.

Dividing the 10-ml sample volume in the conventional method between two bottles could conceivably affect recovery rates for aerobic and anaerobic organisms when compared with recovery for the 10-ml LC tube. However, the unique nature of the LC technique, involving centrifugation, supernatant removal, and inoculation of the remaining sediment onto multiple agar plates, makes strict volume comparisons difficult, since organisms from LC tubes could also conceivably have been plated onto nutrient agar or subjected to atmospheric conditions incapable of sustaining growth. The purpose of these studies was to compare total recovery rates for various organisms between the two different methods. We consider the blood volumes in the two methods equivalent at the outset; thus, we compare the two treatments.

Since organisms detected by the conventional method had no delay associated with their recovery, the mean time calculated for positive isolates detected by the conventional method serves as the expected estimate for comparison with the observed mean delay-in-processing time for positive isolates detected by LC. If delay in processing were detrimental to recovery of organisms by LC, we would have expected the mean for LC-positive isolates to be significantly less than that of conventional-positive isolates. In other words, a significant loss of viability for organisms held in LC cultures might significantly lower the observed mean delay-in-processing time. Our comparison indicates no significant differences between the means for any group of similar organisms. This similarity between the means suggests that organisms in LC survive despite delay in processing; this finding may be confirmed by examining the data in Table 2. These clinical results support the findings of Cashman et al. who found 98% recovery of low numbers of seeded organisms in an in vitro study despite LC delay in processing of 15 h at 34°C (7).

Organisms recovered during this study were those normally considered important causes of bacteremia or fungemia in marrow transplant patients, i.e., members of the *Enterobacteriaceae*, *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., and *Candida* spp. Most of the patients included were studied in the first 100 days after transplantation. Certain organisms, such as *Neisseria* spp. and *Haemophilus* spp., are not common causes of infections during that time period and were not detected during our study.

Pseudomonas spp. and *Candida* spp. accounted for 34% of our total blood culture isolates. Rapid detection of these organisms often associated with infections in immunocompromised patients (2, 8, 22) can conceivably decrease the risk of serious morbidity and mortality by allowing earlier administration of appropriate antibiotic therapy. We have previously noted that relatively slow-growing organisms, such as *Pseudomonas* spp. and *Candida* spp., were detected significantly sooner by LC than by our conventional method (9). In contrast, detection of rapidly growing organisms, i.e., *Streptococcus* spp. and members of the family *Enterobacteriaceae*, was adversely affected by a delay in processing of LC, with time to detection delayed in direct proportion to the delay in processing experienced by these rapidly growing organisms (9).

As expected, blood cultures demonstrating higher numbers of organisms consistently had shorter time to detection by both methods. However, such a strong association could easily confound univariate analysis of mean time to detection. One might reasonably expect a direct relationship between the delay in processing associated with LC and time to detection for all isolates; however, this did not prove to be the case, because time to detection was also dependent on the specific growth characteristics of the organism. Thus, while time to detection appears to be primarily affected by the number of organisms detected, by using a covariate proportional hazards model we were able to account for this effect of CFU per milliliter and demonstrate that time to detection was also dependent on the method of detection as well as organism growth characteristics. Therefore, any association detected between delay in processing and time to detection is not due simply to a mutual association between these factors and CFU per milliliter.

The impact of antibiotics on the detection of various organisms in blood specimens has been previously described (12, 16, 23, 29). The results of our study using LC are consistent with reports of others using the pour-plate culture technique, showing reduced concentrations of organisms in the presence of antimicrobial agents (24, 31). Although the LC technique resulted in recovery of more organisms than the conventional method, this increase occurred both in the presence and absence of effective antibiotics. No difference in the proportion of isolates found at less than or greater than 1 CFU per milliliter was found between the two methods. Although one might expect a reduced yield after a prolonged delay of greater than 8 h for blood specimens collected in the presence of antibiotics, such a reduction did not occur although a trend to lower CFU per milliliter was demonstrated in our study. One study reports that antibiotic concentrations in both biphasic and broth medium are approximately 10-fold lower than those in blood processed by LC (23); however, antibiotic activity in Isolator tubes held for 8 to 24 h at 35°C most certainly would be accompanied by decay in activity dependent on a number of factors, including type of antibiotic, sodium polyanetholesulfonate inactivation, and pH changes. McKenzie and Reimer report that organism recovery is dependent on the ratio of antibiotic concentration in the blood to the MIC of the antibiotic for the organism (21). Since serum antibiotic levels were not determined for patients in our study, we could not accurately determine the influence antibiotics had on individual culture outcome.

In summary, this study showed that delay in processing of LC tubes for up to 24 h did not adversely affect the overall recovery of organisms compared with the results seen with our conventional two-bottle method. This information might be useful for laboratories which do not have 24-h staffing but receive blood cultures at all hours or for those which elect to process the Isolator in batches. However, a detrimental effect on time to detection of certain organisms was seen.

Delay in processing adversely affected the time to detection by LC for streptococci and members of the family *Enterobacteriaceae*, organisms accounting for 16.3% of our total isolates. Prolonged time to detection for these organisms could be problematic if the LC method were to be used as the sole blood culture method and Isolator tubes were to be subjected to appreciable delays in processing.

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