Value of routine procurement of Isolator in addition to BacT/Alert blood cultures in febrile neutropenic patients with acute myeloid leukemia

Tariq A Madani MBBS FRCPC[1], Amin Kabani MD[1,2], Daryl Hoban PhD[1,2], Ruth Loewen RN[1], Eric J Bow MD[1,3]

TA Madani, A Kabani, D Hoban, R Loewen, EJ Bow. Value of routine procurement of Isolator in addition to BacT/Alert blood cultures in febrile neutropenic patients with acute myeloid leukemia. Can J Infect Dis 1998;9(5):287-293.

OBJECTIVE: To evaluate the value of routinely obtaining blood culture with an Isolator system (Isol) along with the BacT/Alert (BT) system from febrile neutropenic patients with acute myeloid leukemia (AML).
METHODS: When an infection was suspected, one aerobic BT bottle from each lumen of double or triple lumen central lines and one anaerobic BT and one Isol tube from a peripheral vein were obtained. The three to four BT bottles and one Isol tube constituted one set of blood culture.
RESULTS: Of the 291 sets obtained, microorganisms were isolated from 94 sets (32%), of which 68% (64 of 94) were considered pathogens and 32% (30 of 94) contaminants. Of the pathogens, 51% were detected by BT only and 16% by Isol only. There were nine episodes of candidemia; eight detected by BT only and none by Isol only. Of 56 Gram-positive cocci and nine Gram-negative bacilli, 50% and 67% were detected by BT only and 16% and none by Isol only, respectively. Contamination rates were 2.4% and 11.7% for BT and Isol, respectively ($P<0.0001$).
CONCLUSIONS: Routine procurement of Isol in addition to BT blood culture was of limited value and was associated with a high rate of contamination, the consequences of which may be deleterious in the immunocompromised host.

Key Words: *Acute myeloid leukemia, BacT/Alert system, Blood culture, Febrile neutropenia, Isolator system*

Valeur de l'obtention systématique d'hémocultures avec le système Isolator associé au système BacT/Alert chez les patients neutropéniques fébriles atteints d'une leucémie myéloïde aiguë

OBJECTIF : Évaluer la valeur de l'obtention systématique d'hémocultures avec le système Isolator (Isol) associé au système BacT/Alert (BT) pour les patients neutropéniques fébriles atteints d'une leucémie myéloïde aiguë (LMA).
MÉTHODES : Lorsque l'on soupçonnait la présence d'une infection, on a recueilli un flacon de sang, pour la culture en

voir page suivante

[1]Departments of Medicine and Medical Microbiology, the University of Manitoba; [2]The Clinical Microbiology Laboratory, Health Sciences Centre; [3]The Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba
Correspondence: Dr Tariq Ahmed A Madani, Department of Internal Medicine, King Abdulaziz University Hospital, PO Box 6615, Jeddah 21452, Saudi Arabia. Telephone 9662-640-1000, fax 9662-640-3975, e-mail tmadani@kaau.edu.sa
Recieved for publication February 28, 1997. Accepted June 11, 1998

aérobie avec le système BT, de chaque lumière des cathéters centraux à double ou à triple lumières, et un du système BT pour la culture en anaérobie puis, une éprouvette pour le système Isol à partir d'une veine périphérique. Les trois à quatre flacons du système BT et l'éprouvette du système Isol ont constitué un lot d'hémocultures.

RÉSULTATS : Des 291 lots obtenus, des micro-organismes ont été isolés de 94 lots (32 %), dont 68 % (64/94) étaient considérés pathogènes et 32 % (30/94) contaminants. Des pathogènes, 51 % ont seulement été décelés par le système BT et 16 % seulement par le système Isol. Neuf épisodes de candidémie sont survenus ; huit seulement décelés par le système BT et aucun par le système Isol. De 56 cocci Gram positif et de 9 bacilles Gram négatif, respectivement 50 % et 67 % ont été décelés uniquement par le système BT, et 16 % et aucun par le seul système IsoL. Les taux de contamination étaient respectivement de 2,4 % et de 11,7 % ($p<0,0001$) pour les systèmes BT et Isol.

CONCLUSIONS : L'obtention d'hémocultures qui fait appel à l'utilisation conjointe des deux systèmes Isol et BT a eu une valeur limitée et a été associée à un fort taux de contamination, dont les conséquences peuvent nuire aux patients immunodéprimés.

Patients receiving cytotoxic therapy for acute myeloid leukemia (AML) are at high risk for infections caused by bacteria and fungi (1). Many studies have suggested that the lysis-centrifugation (Isolator, Isostat, Wampole Laboratories, New Jersey) blood culture system is superior to standard systems for the recovery of opportunistic yeasts, Gram-positive cocci, and to a lesser extent certain Gram-negative bacteria (2-12). Recent studies have shown that the Isolator system is superior to the BacT/Alert (Organon Teknika Inc) system for the recovery of fungi (13,14). These two systems are often used in parallel, especially in immunocompromised patients who are at high risk for fungemia, and disseminated fungal and other opportunistic infections. Data supporting this practice are lacking, however. Accordingly, we evaluated the value of routinely obtaining Isolator cultures in addition to the standard BacT/Alert cultures from febrile neutropenic patients with AML receiving cytotoxic therapy and ciprofloxacin antimicrobial prophylaxis with respect to the relative frequencies of isolation of pathogenic microorganisms and of contamination.

PATIENTS AND METHODS

A total of 333 blood culture sets were obtained during 129 febrile neutropenic episodes in 42 patients who received repeated courses of induction, consolidation, salvage or bone marrow transplant conditioning chemotherapy for AML between January 1992 and December 1994.

A blood culture set consisted of 20 mL of blood obtained by peripheral venepuncture inoculated as two 10 mL aliquots into one Isolator and one anaerobic BacT/Alert bottle, and a 10 mL blood sample obtained from each lumen of the double or triple lumen central venous catheter inoculated into aerobic BacT/Alert bottles. Thus, one blood culture set consisted of 40 to 50 mL of blood. After collection, all samples were transported to the microbiology laboratory. Samples received between 08:00 and 23:00 were immediately processed, whereas those received after 23:00 were incubated at 35°C and then processed at 08:00 the next morning.

The Isolator tubes were processed as directed by the manufacturer. Briefly, the Isolator tube was centrifuged, and the supernatant was discarded. The sediment from the Isolator tube was inoculated onto five agar plates: chocolate blood agar incubated at 35°C in 5% carbon dioxide for five days with daily inspection, blood agar with vitamin K incubated anaerobically at 35°C for five days with inspection every other day, and three fungal media (inhibitory mold agar, brain heart infusion blood agar and Sabhi medium) incubated at 30°C for six weeks with inspection daily for the first two weeks and then twice weekly for the remaining four weeks.

The BacT/Alert microbial detection system is an automated broth-based test system capable of continuously monitoring aerobic and anaerobic blood culture specimens. This system is based on detection of carbon dioxide produced by the metabolism of growing microorganisms (15). The vented aerobic and the unvented anaerobic BacT/Alert bottles were incubated in the BacT/Alert cabinet for five days. A positive result was signaled immediately upon detection by the instrument. Aliquots obtained from the positive bottles were Gram stained and subcultured onto sheep blood agar incubated at 35°C, chocolate blood agar incubated at 35°C in 5% carbon dioxide, and blood agar with vitamin K incubated anaerobically at 35°C. Aliquots from the negative bottles of the same set were also Gram stained and subcultured onto similar media if the Gram stain showed microorganisms, otherwise the bottles were reincubated for the remainder of the five days and then discarded.

Time to detection was defined by the interval in days between the time that the cuture was obtained and the time that the first culture was detected. Data from all the negative and positive BacT/Alert and Isolator blood culture sets were retrieved from the BacT/Alert computer database and from patients' charts.

All patients were assessed by the infectious diseases consult service upon their admission to the hematology/oncology unit before receiving chemotherapy and throughout their course in hospital. Charts of all patients were reviewed by one of the authors to determine the clinical significance of each isolate.

A number of parameters were used in the assessment of clinical significance of isolated microorganisms including the presence of fever, chills or shock; the presence or absence of a likely source of infection; the number of positive bottles per blood culture set; the number of sites or blood culture sets from which the same microorganism was isolated during the same febrile episode; the type and number of isolates; the time to detection; the number of colonies on the solid media planted from Isolator tubes; the response to therapy; and the opinions of the infectious diseases consultants and the hematology/oncology attending physicians who were following the patient. If more than one blood culture set was obtained during a febrile episode, each set was evaluated separately. Criteria used to designate a microorganism as a pathogen regard-

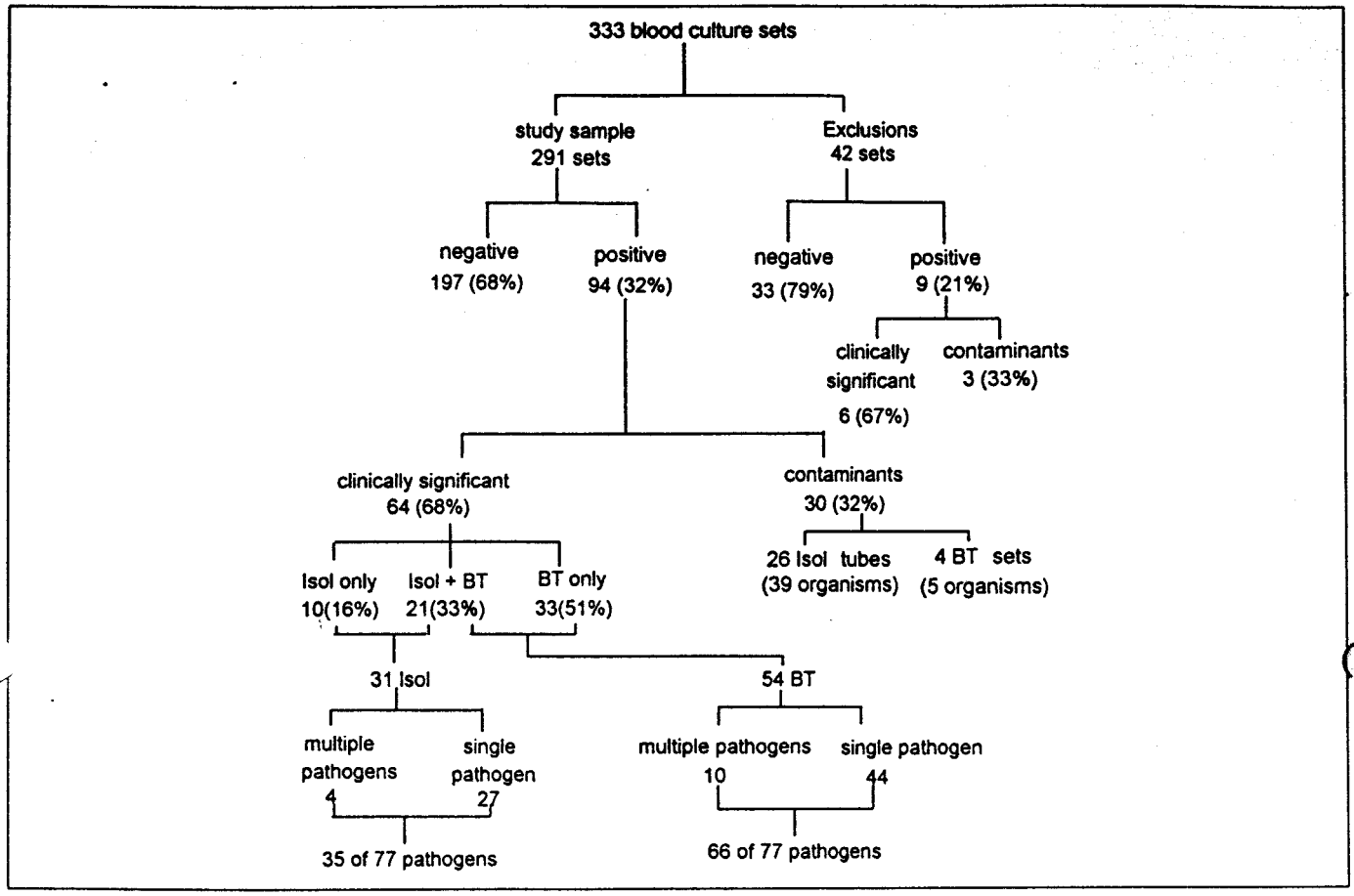

Figure 1) *Schematic summary of the results of the comparison of Isolator (Isol) (Isostat, Wampole Laboratories, New Jersey) and BacT/Alert (BT) (Organon Teknika Inc) blood culture techniques*

less of its type included detection of the same microorganism from two or more BacT/Alert bottles, detection of the same microorganism from the Isolator tube and one or more BacT/Alert bottle, or detection of the same microorganism from two or more blood culture sets obtained during the same febrile episode. The clinical significance of isolates recovered from single BacT/Alert bottles or Isolator tubes was based on the genus and species of a microorganism and its potential pathogenicity (16-19). Three categories of microorganisms were thus defined. Definite pathogens (16) included *Staphylococcus aureus*, *Enterococcus* species, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, Gram-negative bacteria and *Candida* species. These microorganisms were considered pathogens unless the patient's clinical status was completely stable, the patient had no potential source for the microorganism and there was no more than one colony of the isolate on no more than one of the five solid media inoculated from the Isolator tube, or the time to detection of a microorganism was extraordinarily long. Potential pathogens (16,17,19) included coagulase-negative staphylococci and viridans streptococci. These microorganisms were considered pathogens if they were associated with a clinically infected site as the potential source. For example, an association between an inflamed central venous catheter site and the isolation of a coagulase-negative staphylococcus or a severe oropharyngeal mucositis and the isolation of a viridans group streptococcus. Contaminants included *Micrococcus* species, diphtheroids, *Propionibacterium* species, *Bacillus* species, *Streptomyces* species, *Penicillium* species, *Aspergillus* species and *Cladosporium* species. A microorganism from this group was considered a pathogen only if it was isolated from at least two BacT/Alert bottles, from the Isolator tube and one or more BacT/Alert bottle, or from two separate sets obtained during the same febrile episode.

All patients except one received oral ciprofloxacin for prophylaxis against Gram-negative infection starting on day one of chemotherapy and stopping after the recovery of absolute neutrophil count (ANC) to more than 0.5×10^9/L. One patient did not receive prophylactic antibiotics due to ciprofloxacin and cotrimoxazole hypersensitivity.

The statistical significance of categorical and continuous data was tested using McNemar's test for correlated proportions and the two-tailed *t* test, respectively. Significance was defined as $P<0.05$.

RESULTS

The duration of febrile episodes ranged from two to 30 days, and the number of blood culture sets obtained during each episode ranged from one to 10 sets (mean 3±2 sets per febrile episode). Of the 333 blood culture sets, 237 sets (71%) were obtained during severe neutropenia (ANC less than 0.5×10^9/L). Forty-two of the 333 blood culture sets were excluded from the analysis because Isolator tubes were not ob-

TABLE 1
Clinically significant organisms according to blood culture system

Organism	Total	Number of organisms detected by Both	BacT/Alert only	Isolator only
Fungi	11	1	8	2
Candida species	9	1	8	0
Candida albicans	6	1	5	0
Candida krusei	2	0	2	0
Candida lusitaniae	1	0	1	0
Cryptococcus laurentii	2	0	0	2
Gram-positive organisms	57	20	28	9
Viridans streptococci	15	3	10	2
Staphylococcus epidermidis	15	6	7	2
CNS not epidermidis	14	5	7	2
Micrococcus	4	2	1	1
Staphylococcus aureus	5	1	2	2
Streptococcus agalactiae	1	1	0	0
Streptococcus pneumoniae	1	1	0	0
Enterococcus faecalis	1	0	1	0
Clostridium perfringens	1	1	0	0
Gram-negative bacilli	9	3	6	0
Enterobacter cloacae	2	1	1	0
Klebsiella pneumoniae	2	1	1	0
Klebsiella oxytoca	1	0	1	0
Pseudomonas aeruginosa	1	1	0	0
Stenotrophomonas maltophilia	3	0	3	0
Total number of microorganisms (number of blood culture sets)	77 (64)	24 (21)	42 (33)	11 (10)

CNS Coagulase-negative staphylococci

tained. Microorganisms were isolated from 94 (32%) of the 291 blood culture sets. Of these 94 positive sets, 64 (22% of the total study sample) were considered clinically significant and 30 (10% of the total study sample) were considered contaminants (Figure 1). Of the 64 clinically significant positive sets, 33 (51%) were detected only by BacT/Alert, 10 (16%) only by the Isolator, and 21 (33%) by both systems. Isolates classified as significant are presented in Table 1 according to blood culture system from which they grew. Of the 30 sets that grew contaminants only, four were BacT/Alert sets (13%) and 26 were Isolators (87%). Further, of the 54 BacT/Alert sets and the 31 Isolator tubes that grew clinically significant pathogens, three BacT/Alert sets and eight Isolator tubes also grew microorganisms which were subsequently classified as contaminants. Thus, the overall contamination rate of the 291 blood culture sets was 2.4% (four plus three of 291) and 11.7% (26 plus eight of 291) for the BacT/Alert and the Isolator systems, respectively ($P<0.0001$). Table 2 shows the isolates classified as contaminants according to the blood culture system from which they grew.

The 54 clinically significant positive BacT/Alert sets detected 66 pathogens. Ten (19%) of these sets contained multiple isolates (two isolates, eight sets; three isolates, two sets) and the remaining 44 sets (81%) contained only single isolates. The 31 clinically significant positive Isolator tubes detected 35 pathogens. Four (12%) of these sets contained two isolates, and the remaining 27 (88%) contained single isolates.

Seven patients had nine episodes of candidemia (six *Candida albicans*, two *Candida krusei*, and one *Candida lusitaniae*). Eight (89%) of these episodes were detected by the BacT/Alert system only, and none was detected by only the Isolator system. One episode (*C albicans*) was detected by both systems. One patient had *Cryptococcus laurentii* isolated twice, four days apart, during the same febrile episode while receiving amphotericin B. One blood culture set (four BacT/Alert bottles and one Isolator tube) obtained from this patient before commencing amphotericin B was negative. Both episodes of *Cryptococcus laurentii* fungemia were detected only by the Isolator system after six and 30 days of incubation, respectively. BacT/Alert bottles obtained concomitantly were negative after five days of incubation. This opportunistic yeast was considered a pathogen because it was isolated from two separate blood culture sets obtained during the same febrile episode.

Gram-positive cocci were the most common isolates and comprised 57 of 77 (74%) clinically significant microorganisms isolated. Viridans streptococci (15 of 77, 19.5%), *Staphylococcus epidermidis* (15 of 77, 19.5%) and other coagulase-negative staphylococci (14 of 77, 18%) were the most common. Half (28 of 57) of the Gram-positive cocci were detected by the BacT/Alert system only, 16% (nine of 57) were detected by the Isolator system only, and 35% (20 of 57) by both systems.

Gram-negative bacilli accounted for only 12% (nine of 77) of all microorganisms. Six of the nine (67%) Gram-negative

TABLE 2
Contaminating organisms detected by BacT/Alert and Isolator systems

Organisms	Total	BacT/Alert	Isolator
Staphylococcus epidermidis	14	5	9
Coagulase-negative staphylococcus not epidermidis	12	2	10
Micrococcus	6	2	4
Viridans streptococci	5	0	5
*Enterococcus faecalis**	1	0	1
Nonhemolytic streptococcus, not group D	1	0	1
Diphtheroids	6	0	6
Propionibacterium species	1	1	0
Bacillus species	2	0	2
Streptomyces species	2	0	2
*Acinetobacter lwofii**	2	0	2
*Enterobacter agglomerans**	1	0	1
Neisseria species*,†	2	0	2
Penicillium species	2	0	2
Aspergillus niger	1	0	1
A illus species	1	0	1
*ida paraspilosis**	1	0	1
Cladosporium species	1	0	1
Total number of microorganisms (number of blood culture sets)	61	10 (7 sets)	51 (34 tubes)‡

*See text for the reasons why these isolates were considered contaminant; †Neisseria species other than Neisseria gonorrhoeae and Neisseria meningitidis; ‡$P<0.0001$

bacillemias were detected by the BacT/Alert system only, none by the Isolator system only, and three (33%) by both systems. The nine isolates were recovered during five febrile episodes experienced by five patients who were not receiving ciprofloxacin prophylaxis at the time of bacteremia (ANC greater than 0.5×10^9/L).

The BacT/Alert system and Isolator system detected Gram-positive cocci at a mean (±SD) of 1.1±0.7 days and 1.7±1.1 days, respectively ($P<0.01$), and Gram-negative bacteria at a mean (±SD) of 1.1±0.6 days and 1.3±0.6 days, respectively ($P=0.4$). The nine candida isolates were detected by the BacT/Alert system at a mean (±SD) of 2.1±0.6 days. Th ingle isolate of *C albicans* detected by both the E /Alert and the Isolator systems grew at two and four days, respectively.

A comparison of isolation rates for the single peripheral BacT/Alert bottle and the Isolator showed a trend for higher recovery with the BacT/Alert system of *Candida* species (BacT/Alert, three of nine, Isolator zero of nine, both one of nine; $P=0.25$), viridans streptococci (BacT/Alert eight of 15, Isolator two of 15, both three of 15; $P=0.1$) and total pathogens (BacT/Alert 21 of 77, Isolator 13 of 77, both 22 of 77; $P=0.1$).

Forty-two BacT/Alert blood culture sets were excluded from the analysis because Isolator tubes were not obtained in parallel. Nine of the 42 (21%) excluded sets were positive. Six sets (14.3%) grew clinically significant isolates. Single isolates grew in five sets (*Citrobacter freundii*, *C lusitaniae*, *C albicans*, coagulase negative staphylococcus not epidermidis and *Enterobacter cloacae*) and one sets had two isolates (*Escherichia coli* and *Klebsiella pneumoniae*). Three of the 42 (7.2%) sets grew microorganisms considered to be contaminants (*S epidermidis*, coagulase-negative staphylococcus not epidermidis and a diphtheroid).

In five cases, microorganisms otherwise considered as pathogens were classified as contaminants for the following reasons. One colony of *Candida parapsilosis* was detected after 21 days of incubation on one of the five solid media planted from an Isolator tube obtained from a patient who developed fever on day 20 of empirical amphotericin B therapy. The patient had mucositis and no evidence of invasive candidiasis. Viridans streptococcus was isolated from all four BacT/Alert bottles and this Isolator tube after one day of incubation. The fever was considered to be due to viridans streptococcus bacteremia that responded well to antibacterial therapy. One colony of *Enterococcus faecalis* and *Neisseria subflava*, and two colonies of viridans streptococcus were detected after three days of incubation, on one of the five solid media planted from an Isolator tube that was obtained from a patient with disseminated trichosporonosis proven by liver and skin biopsy. A subsequent set of blood cultures obtained two days later grew *Acinetobacter lwoffii* and coagulase-negative staphylococci on one of the five solid media planted from the Isolator tube after four days of incubation. All four BacT/Alert bottles were negative. The four bacterial isolates were considered contaminants, and the patient improved with amphotericin B therapy only. An Isolator culture from another patient grew *A lwoffii* as a single colony along with three other contaminants (two colonies of two morphotypes of *Staphylococcus warneri*, and one colony each of *Staphylococcus carnosus* and a diphtheroid) after four days of incubation on one of the five plates. The four BacT/Alert bottles were negative, and the patient was clinically stable. One colony of *Enterobacter agglomerans* and one colony of *Penicillium* species were detected after five days of incu-

bation on one of the five plates planted from an Isolator tube obtained from a patient after four days of therapy with imipenem and vancomycin for *S epidermidis* bacteremia and biopsy-proven pyogenic liver abscesses. BacT/Alert bottles obtained concomitantly were negative. Imipenem was discontinued on the day that the culture was obtained, and the patient improved on vancomycin alone. A pregnant patient with a newly diagnosed AML developed a high grade fever 24 h after induced vaginal delivery. *Streptococcus agalactiae* (group B streptococcus) was recovered from all BacT/Alert bottles and the Isolator plates within 24 and 48 h of incubation, respectively. Urine culture was also positive for the same microorganism. The patient's bacteremic infection was thought to be caused by a *S agalactiae* urinary tract infection, which responded well to antibiotics. Subsequently, after seven days of incubation, *Neisseria* species (neisseria other than *N meningitidis* and *N gonorrhoeae*) and a viridans streptococcus were detected on one of the five plates planted from the Isolator tube. These two isolates were considered contaminants.

DISCUSSION

Over the past decade, the spectrum of pathogens that cause bacteremic infections in neutropenic patients has changed dramatically. Gram-positive microorganisms have become the most common pathogens, whereas Gram-negative bacilli are less frequently isolated (17-25). Fungal infections and fungemia remain the second major cause of infection-related morbidity and mortality in this population of patients (26-30).

Many factors affect the ability to isolate pathogens from the blood, including the type of media and the method used for culture, the volume of blood sampled, the duration of incubation, and the presence of antimicrobials in the circulation at the time of culture. Several studies have suggested that the Isolator system is superior to conventional broth system for the recovery of *E coli* and yeasts (2); to Tryptic Soy broth (Difco Laboratories, Michigan) for *S aureus*, yeast and enterococci (3); to biphasic Trypticase broth (BBI Microbiology Systems, Maryland) and agar for the facultative Gram-negative bacilli (4); to biphasic brain heart infusion for fungi (5); to the Roche Septi-Chek (New Jersey) system for *S aureus* and *Enterobacteriacae* (6); to the nonresin Bactec radiometric system for yeast, *Enterobacteriacae* and *Staphylococcus* species (7,8); and to the biphasic Roche Septi-Chek broth system for *S aureus* (9). Incorporation of resin into blood culture systems (radiometric and nonradiometric BACTEC and the Antimicrobial Removal Device systems (Marion Scientific, Missouri) has been shown to improve their efficiency to equal that of the Isolator system for the recovery of yeast, *S aureus* and facultative Gram-negative bacilli (10-12). Recent studies comparing the Isolator and BacT/Alert systems have suggested superior performance of the Isolator system for the detection of fungi and *S aureus* (13,14).

The volume of blood drawn in adults is the most important factor that affects the sensitivity of blood cultures. The sensitivity increases 3% to 3.2% for each additional millilitre of blood obtained. Ten to 20 mL of blood per draw has been recommended (31).

In the present study, we obtained 30 to 40 mL of blood for culture using the BacT/Alert system. This approach detected all cases of candidemia and Gram-negative bacteremia, and most (84%) cases of Gram-positive bacteremia. On the other hand, the Isolator system missed 89% (eight of nine) of all cases of candidemia, 67% of cases of Gram-negative bacteremia and 50% of cases of Gram-positive bacteremia. Thus, the addition of an Isolator tube to the three to four BacT/Alert bottles did not increase the recovery of *Candida* species from blood cultures in our study. The apparent advantage of the Isolator over the BacT/Alert system in detecting *C laurentii* fungemia may have been simply related to the longer incubation time of the Isolator system (45 versus five days). The recovery of nine of 57 pathogenic Gram-positive cocci by the Isolator only could simply be accounted for by the extra volume of blood (10 mL) cultured.

The better performance of the three to four BacT/Alert bottles over the Isolator system was likely largely due to the larger total blood volume cultured (30 to 40 mL versus 10 mL). Interestingly, when the difference in volume was corrected by comparing the single peripheral BacT/Alert bottles with Isolator tubes that were obtained from the same peripheral venepuncture; the Isolator missed three cases of candidemia that were detected by the peripheral BacT/Alert bottles and none of the *Candida* species was detected by the Isolator system alone. The presence of ciprofloxacin in the blood sample inoculated into the Isolator tube may have confounded the performance of the Isolator system in detecting bacterial pathogens because of the lack of any significant dilution effect compared with that of the BacT/Alert bottles, which contain 40 mL of broth.

The Isolator system had a significantly higher rate of contamination, which, in immunocompromised patients, only confuses the clinical picture and poses uncertainty about the clinical significance of the isolated microorganisms that would otherwise be considered contaminants in normal hosts. This may lead to unnecessary use of certain antimicrobials such as vancomycin.

CONCLUSIONS

Our results indicate that in patients with AML receiving totoxic therapy and ciprofloxacin prophylaxis, the routine use of the Isolator in addition to the BacT/Alert system for blood culture was of limited value. The high rate of contamination associated with the Isolator system is of particular concern, especially in the immunocompromised host. The routine use of Isolator system in conjunction with the BacT/Alert system is, therefore, not recommended. If slow growing microorganisms are suspected, one should incubate the BacT/Alert bottles for an appropriately longer period of time and, if necessary, perform terminal subculture.

ACKNOWLEDGEMENTS: The assistance of the senior technologist Joan Koss is gratefully acknowledged. We thank Mary Cheung for her assistance with statistical analysis.

REFERENCES

1. Schimpff SC, Young VM, Greene WH, Vermeulen GD, Moody MR, Wiernik PH. Origin of infection in acute nonlymphocytic

leukemia: Significance of hospital acquisition of potential pathogens. Ann Intern Med 1972;77:707-14.
2. Kiehn T, Wong B, Edwards FF, Armstrong D. Comparative recovery of bacteria and yeast from lysis-centrifugation and a conventional blood culture system. J Clin Microbiol 1983;18:300-4.
3. Henry NK, McLimans CA, Wright AJ, Thompson RL, Wilson W, Washington JA II. Microbiological and clinical evaluation of the Isolator lysis-centrifugation blood culture tube. J Clin Microbiol 1983;17:864-9.
4. Kelly MT, Buck GE, Fojtasek MF. Evaluation of a lysis-centrifugation and biphasic bottle blood culture system during routine use. J Clin Microbiol 1983;18:554-7.
5. Bille J, Edson RS, Roberts GD. Clinical evaluation of the lysis-centrifugation blood culture system for the detection of fungemia and comparison with a conventional biphasic broth blood culture system. J Clin Microbiol 1984;19:126-8.
6. Henry NK, Grewell CM, Van Grevenhof PE, Ilstrup DM, Washington JA II. Comparison of lysis-centrifugation with a biphasic blood culture medium for the recovery of aerobic and facultatively anaerobic bacteria. J Clin Microbiol 1984;20:413-6.
7. Brannon P, Kiehn TE. Large-scale clinical comparison of the lysis-centrifugation and radiometric system for blood culture. J Clin Microbiol 1985;22:951-4.
8. Ilogg JA, Manzella JP, McConville JH. Clinical laboratory nparison of the 10 mL Isolator blood culture system with ACTEC radiometric blood culture media. J Clin Microbiol 1984;20:618-63.
9. Walker RC, Henry NK, Washington JA II, Thompson RL. Lysis-centrifugation blood culture technique: Clinical impact in *Staphylococcus aureus* bacteremia. Arch Intern Med 1986;146:2341-3.
10. Kelly MT, Roberts FJ, Henry D, Geere I, Smith JA. Clinical comparison of Isolator and BACTEC 660 resin media for blood culture. J Clin Microbiol 1990;28:1925-7.
11. Brannon P, Kiehn T. Clinical comparison of lysis-centrifugation and radiometric resin systems for blood culture. J Clin Microbiol 1986;24:886-7.
12. Moody JA, Fasching CE, Shanholtzer CJ, Gerding DN, Peterson LR. Evaluation of new blood culture processing systems. J Clin Microbiol 1984;20:351-6.
13. Lyon R, Woods G. Comparison of the BacT/Alert and Isolator blood culture systems for the recovery of fungi. Am J Clin Pathol 1995;103:660-2.
14. Hellinger WC, Cawley JJ, Alvarez S, et al. Clinical comparison of the Isolator and BacT/Alert aerobic blood culture systems. J Clin Microbiol 1995;33:1787-90.
15. Thorpe TC, Wilson ML, Turner JE, et al. BacT/Alert: An automated microbial detection system. J Clin Microbiol 90;28:1608-12.
16. einstein MP, Reller LB, Murphy JR, Lichtenstein KA. The linical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 1983; 5:35-53.
17. Winston DJ, Dudnick DV, Chapin M, Winston G, Gale RP, Martin WJ. Coagulase negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 1983;143:32-6.
18. Viscoli C, van der Auwera P, Meunier F. Gram-positive infections in granulocytopenic patients: an important issue. J Antimicrob Chemother 1988;21(Suppl C):149-56.
19. Kern W, Jurrie E, Schmeiser T. Streptococcal bacteremia in adult patients with leukemia undergoing aggressive chemotherapy. A review of 55 cases. Infection 1990;18:138-45.
20. Klastersky J, Zinner SH, Calandra T, et al. Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: Lessons from four EORTC trials. Eur J Cancer Clin Oncol 1988;24:S35-45.
21. Karp JE, Dick JD, Angelopulos C, et al. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Am J Med 1986;81:237-42.
22. Whimbey E, Kiehn TE, Brannon P, Blevins A, Armstrong D. Bactermia and fungemia inpatients with neoplastic disease. Am J Med 1987;82:723-9.
23. EORTC International Antimicrobial Therapy Cooperative Group. Gram-positive bacteremia in granulocytopenic cancer patients. Eur J Cancer Clin Oncol 1990;26;5:569-74.
24. EORTC International Antimicrobial Therapy Cooperative Group. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann Intern Med 1993;119:584-93.
25. Bochud P, Calandra T, Francioli P. Bacteremia due to viridans streptococci in neutropenic patients: A review. Am J Med 1994;97:256-64.
26. Krick J, Remington J. Opportunistic invasive fungal infections in patients with leukemia and lymphoma. Clin Haematol 1976;5:249-310.
27. DeGregorio MW, Lee WMF, Linker CA, Jacobs RA, Ries CA. Fungal infections in patients with acute leukemia. Am J Med 1982;73:543-8.
28 Hawkins C, Armstrong D. Fungal infections in the immunocompromised host. Clin Haematol 1984;3:599-630.
29. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1988;148:2642-5.
30. Bodey G, Bueltmann B, Duguid W, et al. Fungal infections in cancer patients: an international autopsy survey. Eur J Microbiol Infect Dis 1992;11:99-109.
31. Mermel LA, Maki DG. Detection of bacteremia in adults: Consequences of culturing an inadequate volume of blood. Ann Intern Med 1993;119:270-2.