



Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation

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Summary:

Infection remains an important cause of morbidity and mortality after bone marrow or stem cell transplantation. To evaluate the role of obtaining blood cultures for intermittent or persistent fever in neutropenic patients on antibiotic therapy, we performed a retrospective chart review of 196 consecutive patients admitted to the Bone Marrow Transplant Unit at the University of North Carolina Hospitals from 1995 to 1998. From the cohort of 196 patients, 154 patients developed neutropenic fever. The initial blood culture was positive in 16 of 145 patients during the first fever episode giving a prevalence of 11%. From the total of 109 patients that had blood cultures drawn after day 1 of fever, five patients had blood cultures positive for a pathogen, a prevalence of 4.6%. In only one patient, did blood cultures drawn after day 1 identify an organism not present on day 1 (prevalence 0.9%). After reviewing the results in the first 105 patients, we changed our timing of collection of blood cultures. Forty-nine patients were treated in this manner and we found that the mean number of blood cultures decreased from 9.2 to 4.7 per patient without a change in the frequency of infectious complications or length of hospitalization. *Bone Marrow Transplantation* (2000) 26, 533–538.

Keywords: stem cell transplantation; fever; blood culture; neutropenia

High-dose chemotherapy with stem cell or bone marrow transplantation (BMT) is currently used in the treatment of solid tumors,^{1–4} hematological malignancies,^{5–10} and congenital diseases.^{11,12} For both autologous and allogeneic transplantation, bacterial and fungal infections are an important source of early morbidity and mortality.^{13,14}

The clinical hallmark of bacteremia in the febrile neutropenic host has been the development of fever. Studies

performed in the 1970s documented a 20–60% incidence of bacteremia in the febrile neutropenic host.^{15–17} Because of the profound decrement in the absolute neutrophil count, neutropenic patients may not mount a local inflammatory response when infected.^{18,19} As a result, most transplant centers obtain serial blood cultures from patients during neutropenic episodes following an initial fever.²⁰

Recent investigators have noted a sharp decrease in the incidence of bacteremia in the febrile neutropenic host.²¹ We noted a similar decrease in the incidence of bacteremia in patients transplanted at our institution. We also found a low incidence of pathogens on follow-up blood cultures in this patient population. To study this further, we performed a retrospective chart review to assess the clinical information obtained by the persistent collection of blood cultures in febrile neutropenic patients after initiation of empiric antibiotic therapy.

Methods

Study design and definitions

This study was conducted from 1995 to 1998 at the University of North Carolina Hospitals, a 665-bed tertiary care medical center. One hundred and ninety-six patients consecutively admitted to the Bone Marrow Transplant Unit were eligible for inclusion in the study. Patients were excluded for lack of fever, neutropenia or inadequate medical records. Of the 196 patients admitted to the Bone Marrow Transplant Unit, 154 met the inclusion criteria. Forty-two patients were excluded from analysis because of lack of fever $\geq 38.3^{\circ}\text{C}$ ($n = 26$), lack of leukopenia < 1000 cells/ml ($n = 3$) or incomplete medical records ($n = 13$). Of the 154 patients that met the study criteria, 120 patients received an autologous stem cell or marrow transplant and 34 received an allogeneic or unrelated stem cell or marrow transplant.

All patients were housed in either private high efficiency particulate air-filtered (HEPA) rooms or positive pressure reverse isolation rooms. Patients were not permitted to eat raw fruit that could not be peeled or raw vegetables. Caregivers were not allowed to administer therapy via rectal, vaginal or intramuscular routes. All hospital personnel employed strict handwashing procedures with an antimicrobial agent before entering patients' rooms. On admission,

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all patients underwent a posterior and lateral chest radiograph, urinalysis, and had blood drawn for complete blood count, routine electrolytes, and liver function tests. No patients were actively infected at the time of hospital admission.

Patients were given prophylactic antibiotics using standard protocols. Trimethoprim/sulfamethoxazole (160 mg orally twice a day) was administered from day of admission until 2 days prior to the stem cell or marrow infusion. Ciprofloxacin (500 mg orally twice a day) was administered from 1 day prior to the stem cell or marrow infusion until the onset of neutropenic fever.^{22,23} Fluconazole (200–400 mg orally per day) was administered to all patients at the time of admission or 4 days prior to the infusion of stem cells until engraftment.²⁴ Acyclovir was given to all patients who had a positive test for HSV antibodies by enzyme linked immunosorbent assay (ELISA). Filgrastim 5 µg/kg subcutaneously per day was given to all recipients of autologous marrow or stem cells starting on either the day of stem cell or marrow infusion or day 5 after the infusion. Patients receiving allogeneic marrow or stem cells did not routinely receive growth factors. Pediatric patients received intravenous vancomycin as prophylaxis starting 2 days prior to stem cell or marrow infusion.²⁵

The following definitions were used for the study: leukopenia was defined as a white cell count $\leq 1000 \times 10^9/l$. For the nadir white blood cell count, leukopenia was used rather than neutropenia as patients with white cell counts $\leq 500 \times 10^9/l$ did not routinely have a neutrophil count performed. Neutropenia was defined as an ANC $\leq 500 \times 10^9/l$. Fever was defined as an oral temperature $>38.5^\circ\text{C}$ once or 38.3°C twice in a 24-h period unrelated to blood product or amphotericin B administration. Patients with a fever and an ANC $\leq 500 \times 10^9/l$ were given intravenous antibiotics and had ciprofloxacin discontinued. A supra-infection was defined as the isolation of a new pathogen in a patient during systemic intravenous antimicrobial therapy.

The first fever episode was defined as an oral temperature greater than 38.5°C once or 38.3°C twice within a 24-h period. After this episode, if a patient defervesced for a continuous period of 96 h or greater, the initial febrile episode was determined to have resolved. Subsequent temperatures that met the initial definition of fever were considered a new and separate fever episode. Thus, each patient had at least one fever episode. The maximum number of fever episodes in this study was four. Temperature was routinely determined six times a day.

The policy of the Microbiology and Immunology Laboratory at the University of North Carolina Hospitals is to permit only three blood cultures to be collected in a 24-h period. The collection of two or three blood cultures at one time was considered a blood culture set. Thus, after one set of blood cultures was collected, a second set was not obtained from patients who had fevers within 24 h. This instance was not considered as a missed culture set. In contrast, a missed blood culture set occurred if a patient had a fever that was separated by at least 24 h from the previous fever and did not have blood cultures obtained. If blood cultures were not drawn at that time, another missed culture set occurred for fevers that occurred 24 h after that time.

Patients who developed fever during neutropenia were

treated initially with parenteral vancomycin and ceftazidime.^{26–28} All patients had blood cultures drawn from at least two separate ports of an indwelling vascular device at the onset of fever and neutropenia. For each culture drawn through an indwelling vascular device, 20 ml of blood was collected, while 10 ml of blood was collected when drawn from a peripheral vein. Blood cultures could also be obtained from a peripheral vein at the same time under the discretion of the attending physician. A total of 87 peripheral blood cultures were obtained from the initial cohort of patients; no peripheral blood cultures were obtained in the second cohort of patients. Blood was cultured by either the lysis centrifugation (Isolator cultures) technique or in antibiotic-impregnated resin bottles. Blood was cultured on chocolate, blood, blood–brain heart infusion (incubated anaerobically) and brain–heart infusion agar supplemented with 10 µg/µl gentamicin (BacT/Alert system; B-D Microsystems, Cockeysville, MD, USA). The chocolate, blood, blood–brain heart infusion plates and gentamicin-treated brain–heart infusion plates were examined daily for 4 days and then weekly for 3 weeks. The broth bottle was incubated aerobically and continuously monitored for 7 days. Micro-organisms were identified using standard techniques.²⁹

Data was abstracted from the medical records of all patients who were eligible for inclusion. The information included patient name, gender, age, race, first morning peripheral white blood cell count, maximum temperature for each 24-h period, lowest systolic blood pressure for each 24 h period, and all medicines administered. Data on each pathogen isolated was provided by the University of North Carolina Hospitals Clinical Microbiology/Immunology Laboratory. A bloodstream infection was defined using previous guidelines from the Centers of Disease Control and Prevention (CDC) modified for the occurrence of coagulase-negative *Staphylococci*.³⁰

Statistical analysis

The association of potential prognostic factors with the occurrence of bacteremia during first fever was analyzed using the Mann–Whitney log rank test. The association between magnitude of temperature on the first day of fever with the occurrence of bacteremia was analyzed using the Mantel–Haenszel chi square test. *P* values less than or equal to 0.05 were considered significant. All tests were determined using a two-tailed analysis.

Results

The characteristics of the 154 patients are given in Table 1. The mean age of the patients was 43 years. There were 66 males and 88 females. The most common diagnoses leading to BMT were relapsed or refractory non-Hodgkin's lymphoma (33%) and high risk or relapsed acute myelogenous leukemia (18%). The mean duration of leukopenia for all of the patients analyzed was 15 days (range 5–73). Seventy-eight percent of the patients had a single episode of fever during the leukopenic period. The mean number of blood cultures drawn per patient during the period of leukopenia

Table 1 Characteristics of the 154 patients with at least one episode of febrile neutropenia

| | No. | % |
|------------------------|-----------|------|
| Gender | | |
| Male | 66 | 43 |
| Female | 88 | 57 |
| Race | | |
| White | 121 | 79 |
| Non-white | 33 | 21 |
| Age (median and range) | 45 (1–67) | |
| Diagnosis | | |
| ALL | 5 | 3.2 |
| AML | 27 | 17.5 |
| BCA | 20 | 13 |
| CML | 5 | 3.2 |
| HD | 9 | 5.8 |
| MM | 12 | 7.8 |
| Neuroblastoma | 2 | 1.2 |
| NHL | 51 | 33.1 |
| OVCA | 15 | 9.7 |
| Other | 8 | 5.2 |
| Number of fevers | | |
| 1 | 120 | 78 |
| 2 | 29 | 19 |
| 3 | 4 | 3 |
| 4 | 1 | 1 |

BCA = breast cancer; OVCA = ovarian cancer.

was 7.7. The majority of the patients who underwent an autologous stem cell transplant were conditioned with etoposide, carboplatin, cyclophosphamide and 1200 cGy of total body irradiation.³¹ The majority of the patients who received an allogeneic bone marrow transplant were conditioned with busulfan and cyclophosphamide.³²

A standard regimen of antibiotics was initiated for patients that had fevers at the onset of neutropenia. Antibiotic use for the patients entered in this study is shown in Figure 1. Because of the intensity of the conditioning regimen employed in the majority of patients treated, grades III and IV mucositis was present in over 95% of patients. Because of this, 88% of the patients were started on vancomycin and 79% on ceftazidime, in accordance with recent guidelines from the IDSA.³³ Twelve percent of patients were started on an aminoglycoside. Imipenem/cilastatin was used with vancomycin in 10% as initial therapy, while 7% of patients with a prior history of fungal infection were started on amphotericin B at the onset of fever.

After the initiation of empiric antibiotic therapy, changes in the antibiotic regimen were under the discretion of the attending physician. Patients with progressive mucositis during febrile leukopenia were often switched from ceftazidime to imipenem/cilastatin. As is demonstrated in Figure 1, administration of imipenem/cilastatin increased linearly from day 1 of fever (10%) until day 7 (85%) of fever. Amphotericin B was given to 61% of the patients that continued to have fever on day 6 of antibiotic therapy (see Figure 1).

Of the 154 patients evaluated in the study, 145 patients had blood cultures drawn during the first episode of febrile neutropenia (see Figures 2 and 3). Three patients did not have blood cultures drawn during the entire period of evaluation and six patients had blood cultures drawn only on

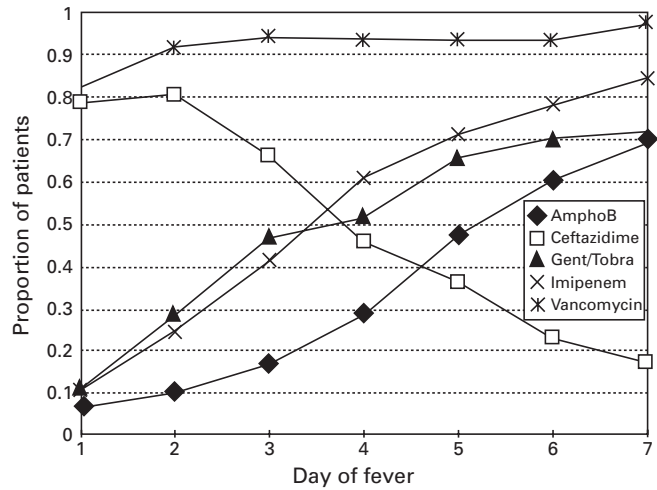


Figure 1 Medication use by day of fever. The proportion of patients receiving the five most commonly used antimicrobial agents is shown as a function of day of fever during the first fever episode. The data is censored after day 7 of the first fever episode due to the paucity of patients who had fever at this time.

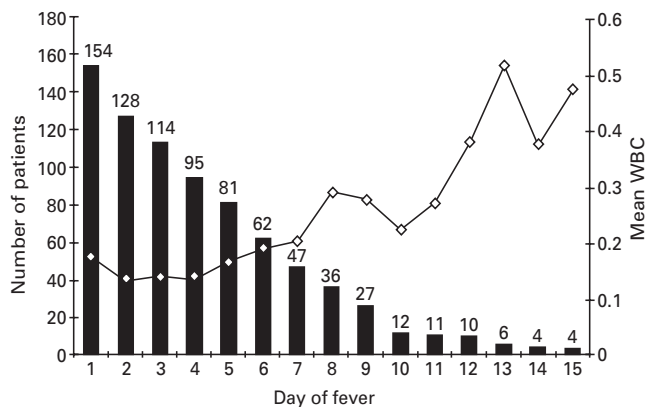


Figure 2 Mean white blood cell count and sample size by day of fever. The number of patients with a fever is shown on the left y axis for each day of fever during the first fever episode. On the right y axis, the mean white count for all patients having fever during the first fever episode is given. The increase in the white cell count at day 8 correlates with early engraftment for patients receiving autologous peripheral blood stem cells. The increase in white cell count at day 12 correlates with engraftment of autologous and allogeneic bone marrow. While 128 patients had fevers on day 2 or later, only 109 patients had blood cultures drawn after day 1.

second or subsequent episodes of fever. From these 145 patients, blood cultures were positive for a pathogen in 16 for a prevalence of 11% (see Table 2).

For the 145 patients who had blood cultures drawn during the first leukopenic fever, blood cultures were drawn in 109 patients sometime after day 1 because of intermittent or persistent fever. There were five patients in whom blood cultures were positive after day 1 of fever for an incidence of 4.6%. The majority of these infectious complications were due to coagulase-negative *Staphylococci*. In one patient, because of the timing of fever, the first blood cultures obtained were positive on day 2 of fever. In three patients, blood cultures were positive both on day 1 of fever and on 1 subsequent day. In one of these patients, the

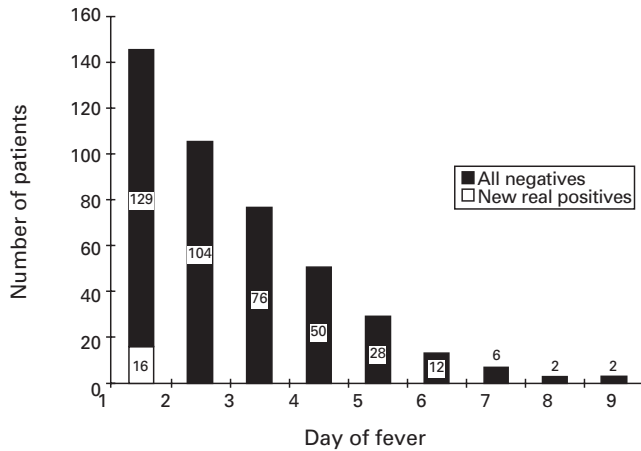


Figure 3 New non-contaminant cultures by culture set. The total number of blood culture sets is shown in the upper region of each bar graph until day 7 when it appears above the bar. Below this in the darker color are the number of new blood culture sets positive for a pathogen. A blood culture set is defined as the collection of two or three blood cultures within 30 min of a febrile episode. Cultures that were positive for the same pathogen on day 1 and any subsequent day are not considered new positive blood cultures for the subsequent day. Contaminating micro-organisms were defined as stated by the CDC guidelines.

Table 2 Organisms cultured from patients in this study

| Organism | No. patients |
|--|--------------|
| Coagulase-negative <i>Staphylococci</i> ^a | 10 |
| <i>Streptococci viridans</i> | 5 |
| <i>Micrococcus/Diptheroidis</i> | 1 |
| <i>Candida</i> sp. | 1 |
| <i>Stomatococcus mucilogensis</i> | 1 |
| Methicillin resistant <i>Staphylococcus aureus</i> | 1 |
| Total | 19 |

^aOrganism cultured on second fever and third fever in one episode respectively. One episode of coagulase-negative *Staphylococci* was cultured on day 2 in a patient that had a fever on day 1 in the evening and blood cultures were not drawn until the following day.

^bOrganism cultured on day 3 when day 1 blood cultures were negative.

indwelling catheter was removed on day 5 of fever because of persistent bacteremia. The other two patients cleared the bacteremia although one patient required prolonged (4 weeks) administration of vancomycin. Blood cultures were positive on day 3, yet negative on day 1 in one patient in which MRSA was cultured. This patient, who had been initiated on therapy with vancomycin, cleared this pathogen by day 5 of fever. For patients with negative blood cultures on day 1, we did not find a positive blood culture after day 3 of fever during the initial febrile episode (see Figure 3).

We also investigated the incidence of positive blood cultures in febrile patients who defervesced for 96 h or more and then had recurrence of fever. There were 40 episodes of recurrent fever (second fever episode or beyond) in 34 patients. Two patients had positive blood cultures for coagulase negative *Staphylococci* on fever episode two and three, respectively, for an incidence of 5.9%.

Because of the paucity of informative data obtained from daily blood cultures in this patient population, we changed

our protocol in the last 49 patients. For this group of patients, blood cultures were drawn on day 1 and then at the onset of antifungal therapy which is typically day 5 of fever at our institution, when changing antibiotic therapy, or for the presence of a pulmonary infiltrate. The number of blood cultures collected per patient was 4.7, which was a 49% reduction from those obtained in the first 105 patients. This decrease was due in part to the lack of blood cultures drawn on febrile days (missed number of cultures in the two groups 2.9 vs 4.7). Despite this decrease in the frequency of obtaining blood cultures, we did not find a difference in the persistence of bacteremia (1.9% in the first cohort vs 2% in the second) after 72 h of antimicrobial treatment, the isolation of a new organism during intravenous antimicrobial therapy (suprainfection rate 1.9% in the first cohort vs 0% in the second cohort) or the time to discharge in the two groups, which was at a median of 31 days for the first cohort and 29.5 days for the second cohort ($P = 0.1$).

Using univariate analysis we attempted to identify risk factors for the occurrence of bacteremia during leukopenic fever in these patients. Total number of blood cultures, total days of fever, age, sex, race, type of transplant and diagnosis prior to transplant were not statistically associated with a day 1 or later positive blood culture. Similar to previously reported data,³⁴ we found a statistical association between the magnitude of fever as a continuous variable and the occurrence of bacteremia only on day 1 ($P = 0.04$).

Discussion

We have evaluated the incidence of positive blood cultures in febrile neutropenic BMT recipients after the initiation of intravenous systemic antibiotics. We found that the initial rate of positive blood cultures in 145 patients was 11%, which is similar to the rate of bacteremia recently reported in this patient population.³⁵⁻³⁸ Additionally, the organisms cultured in this setting were quite similar to those found at another institution using a similar approach.^{22,23}

We performed blood cultures after day 1 of fever in 109 patients evaluated in this study. The incidence of positive blood cultures in this setting was 4.6%. Of those patients with positive blood cultures, three had day 1 blood cultures positive for the same organism and in one patient the day 2 blood cultures were the first collected. In only one patient were follow-up blood cultures positive when day 1 blood cultures had been negative. We found positive blood cultures on second or subsequent fever episodes in 5.9% of patients. In both of these patients, the organism cultured was coagulase negative *Staphylococci*.

One interpretation of these data is that the routine collection of blood cultures after the first day of febrile neutropenia is not helpful. We would strongly disagree with this approach. Had blood cultures not been drawn after the first day of fever, one episode of MRSA would have been missed. Additionally, the collection of blood cultures after day 1 allowed for the identification of one patient who required removal of an indwelling intravascular device because of persistent bacteremia. Thus, we believe that blood cultures should be obtained from all patients after an initial positive

blood culture to document clearance of the pathogen and on day 3 of fever to increase the probability of identifying a pathogen early during treatment. Additionally, we would recommend drawing blood cultures in patients that defervesce after initial antibiotic therapy and then remount a fever. Nevertheless, the widespread use of blood cultures to monitor for an infectious source in febrile neutropenic patients on antibiotic therapy had an extremely low yield in identifying the cause of fever.

Our patients averaged 7.7 blood cultures during the course of leukopenia. This was due to two separate cohorts that were managed differently. In 105 patients, the average number of blood cultures drawn per patient was 9.2. We then changed our protocol to allow for blood culture collection on day 1, and then at the initiation of antifungal therapy (which was typically day 5 of fever), changes in antibiotic therapy or for the presence of a pulmonary infiltrate. In the following 49 patients, the number of blood cultures drawn was 4.7 per patient. There was an increase in the number of blood cultures not drawn despite febrile neutropenia from 2.9 missed cultures in the first 105 patients to 4.7 blood cultures in the next group of 49 patients. Despite the decrease in the number of blood cultures drawn, we did not find an increased incidence of infectious complications or length of stay in the second cohort of 49 patients. A decrease in obtaining 4.5 cultures per patient resulted in an overall savings of approximately \$405 per patient in laboratory costs alone and a reduction in phlebotomy of 85 ml per patient.

One possible criticism of this evaluation is the lack of blood culture data for every febrile day in all patients. If cultures had been drawn for every febrile episode 1438 blood cultures would have been obtained. Only 837 blood cultures were obtained and thus we missed obtaining cultures in 601 instances. Thus, we cannot rule out that had all of the blood cultures been obtained the incidence of bacteremia after day 1 would have increased. We feel that this is unlikely for the following reasons: (1) None of our patients died of unexplained infection suggesting that the incidence of untreated bacteremia was extremely rare; (2) the overwhelming majority of missed blood cultures in the first 105 patients were on the succeeding day after negative blood cultures had been obtained; and (3) physicians had the discretion to draw blood cultures in clinical scenarios that suggested an increased risk of bacteremia. Given the extremely low rate of positive blood cultures, it is likely that physicians decided that the yield of obtaining blood cultures on those missed days was low.

The data from this evaluation confirmed our belief that in clinical practice physicians do not collect daily blood cultures for all episodes of febrile leukopenia. We found that despite not obtaining 49% of the potentially indicated blood cultures in the second group of 49 patients, we did not observe an increase in the incidence of bacterial or fungal infections or a delay in discharge due to infectious complications.

The results of this evaluation should be interpreted cautiously for other transplant programs that do not have a similar patient population or employ similar methods of care. Only one patient evaluated received either an unrelated bone marrow transplant or one antigen MHC-mis-

matched transplant from a family member. Thirty-two patients received an allogeneic MHC matched transplant and the overwhelming majority of the patients ($n = 120$) received an autologous bone marrow or stem cell transplant. Thus, whether these findings would pertain to patients receiving an allogeneic or unrelated bone marrow transplant will have to be verified with a greater number of patients.

While guidelines exist for the management of febrile neutropenia, these guidelines are not dogmatic as to which day antibiotics should be changed in patients with fever and the agents to be used. Changes in antibiotic care in this study were at the discretion of the attending physician. Thus, we did not have a protocol to guide changes in antibiotic therapy, although the majority of patients that remained febrile were switched to imipenem/cilastatin and received amphotericin B. In addition, we did not routinely discontinue the use of vancomycin in patients with negative blood cultures on day 1. In other institutions, routine changes in antibiotic management might not occur in the absence of changes in clinical parameters. Thus, these findings may not apply in institutions in which antibiotic changes are not performed routinely or vancomycin is discontinued after 72 h of treatment.

In conclusion, we have found that the number of positive blood cultures at the onset of fever and neutropenia was 11%. After the initiation of parenteral antibiotics, the incidence of positive blood cultures was 4.6%. In most of these instances, the day 1 blood culture demonstrated the same organism as the follow-up cultures. Thus, in only one instance did follow-up cultures during the first fever episode identify a pathogen not found on day 1 blood cultures. We have shown in 49 patients that an approach in which blood cultures are obtained on day 1 of fever and then for changes in antifungal or antibacterial coverage or for the presence of a pulmonary infiltrate can decrease the number of blood cultures by 49% without jeopardizing patient care.

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