Blood Cultures in the Critical Care Unit*

Improving Utilization and Yield

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Sepsis is a common cause of morbidity and death in critically ill patients, and blood culture samples are often drawn in an effort to identify a responsible pathogen. Blood culture results are usually negative, however, and even when positive are sometimes difficult to interpret. Distinguishing between true bacteremia and a false-positive blood culture result is important, but complicated by a variety of factors in the ICU. False-positive culture results are costly because they often prompt more diagnostic testing and more antibiotic prescriptions, and increase hospital length of stay. A number of factors influence the yield of blood cultures in critically ill patients, including the use of antibiotics, the volume of blood drawn, the frequency with which culture samples are drawn, and the site from which the culture samples are taken. Skin preparation techniques, handling of the cultures in the microbiology laboratory, and the type of blood culture system employed also influence blood culture yield. Attempts to identify predictors of true bacteremia in critically ill patients have been disappointing. In this review, we discuss factors that influence blood culture yield in critically ill patients, suggest ways to improve yield, and discuss true bacteremia vs false-positive blood culture results. We also discuss the costs and consequences of false-positive blood culture results, and list noninfectious causes of fever in the ICU. ***(CHEST 2002; 122:1727–1736)***

Key words: bacteremia; blood cultures; critically ill; ICU; sepsis

Abbreviation: SPS = sodium polyanetholsulfonate

Sepsis, a systemic inflammatory response to infection, is an important cause of morbidity and mortality in critically ill patients, resulting in frequent diagnostic testing, greater prescription of antibiotics, and increased length of hospitalization. In a prospective multicenter study[1] of critically ill patients, clinically suspected sepsis occurred in approximately 9% of adults admitted to ICUs and had a mortality rate of up to 60%. However, microbiological infection was documented in only 71% of patients with suspected severe sepsis, and bacteremia was documented in 53%. Bacteremia (including fungemia) in critically ill patients has an average attributable mortality of 26%,[2] with Candida spp[3] and enterococci[4] responsible for 38% and 31% of mortality, respectively.[5] However, the microbiologic diagnosis of bacteremia acquired after admission is often difficult in the ICU, complicated by the fact that many critically ill patients receive empiric antibiotic therapy. In fact, antibiotic consumption is 10 times greater in ICUs than on general hospital wards.[6] The significant health and potential economic impact of bacteremia underscore the importance of early detection and treatment of nosocomial infections in critically ill patients.

Blood cultures are the standard for diagnosing bacteremic episodes. Critically ill patients are at increased risk of acquiring nosocomial bacteremia because of their underlying disease processes, and because of the presence of invasive devices such as endotracheal tubes and central venous catheters. Of 111 consecutive episodes of nosocomial bacteremia in a medical-surgical ICU during a 36-month period, IV catheter infections were the most common sources of bacteremia. Coagulase-negative staphylococcus and *Staphylococcus aureus* were the most commonly isolated organisms. The overall mortality rate of patients with nosocomial bacteremia has been reported to be 31.5%.[7] Because of the increased risk and associated high mortality of bacteremia, there is generally a low threshold for drawing blood culture samples in the ICU. Unfortunately, the overall yield of blood cultures is low.[8] To increase the efficiency with which blood culture samples are obtained, a number of investigators have tried to identify pre-

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dictors of bacteremia.[9–17] However, there is currently no consensus on acceptable predictors of bacteremia in critically ill patients. In addition, up to 50% of positive blood culture results represent contamination of the culture, rather than true bacteremia,[8,18–20] and distinguishing between true-positive culture results and contaminant cultures is often difficult.

In this article, we review the utilization and diagnostic yield of blood cultures in the ICU, and report the incidence of contaminated blood cultures and their economic impact. We explore potential predictors of bacteremia and highlight means of improving blood culture yield.

Utilization and Yield of Blood Cultures in the ICU

The utilization of blood cultures varies according to physician experience and an estimation of the probability of bacteremia in a given patient population. While there is no good estimate of the number of blood culture samples drawn in ICU settings on a monthly basis, there is some suggestion that this number is excessive. This is especially true in teaching hospitals, perhaps due to the inexperience of house-officers.[21] In a study in a medical ICU, Gross et al[22] implemented a protocol to limit the number of blood culture samples drawn during a 3-week period. Solitary blood culture samples were eliminated. Four blood culture sets were recommended for clinical suspicion of endocarditis, drawn 30 min to 1 h apart. For all other suspected cases of bacteremia, up to three blood culture sets were permitted. In patients with no change in their clinical status and with initially negative blood culture results, no further samples were drawn despite persistent fever. Study results were compared to a representative 3-week period prior to initiation of the protocol. During the study, the number of blood cultures ordered for suspected septic episodes decreased from 3.0 to 2.2 sets. The number of blood culture samples drawn was reduced from 1.2 cultures per discharge to 0.3 cultures per discharge with no untoward effects on patient care.[22] A follow-up survey was conducted 2 months later, at a time when new residents rotating through the ICU were not familiar with the study protocol. Once again, an increase in the number of blood cultures per suspected septic episode was observed.

Despite a tendency to obtain repeated blood cultures in ICUs across the country, the overall yield is often disappointing. In a study of 645 admissions to a trauma and surgical ICU over a 1-year period, 32% of patients had at least one set of blood culture samples drawn while in the ICU. Of these culture results, only 7.5% were positive, and only 4% represented true bacteremia. All fungi, Gram-positive cocci, and Gram-negative rods were considered pathogens if they grew from two or more blood cultures or if they were isolated from another infectious focus (sputum, urine, wound) in addition to blood. Coagulase-negative staphylococci were considered pathogenic if there was evidence of urinary tract, CNS, or vascular catheter infection within 48 h of the blood culture. Bacillus, Micrococcus, and Proprionibacterium spp were regarded as contaminants.[21] The most frequent causes of bacteremia in this study were catheter-related infections, and coagulase-negative staphylococci were the most frequent isolates. The overall incidence of true bacteremia was 3.6 per 100 ICU admissions. Similarly, in another study of septic patients in a surgical ICU, the incidence of positive blood culture results was 3.2 per 100 ICU admissions.[23] In this study, sepsis was defined as a systemic inflammatory response syndrome associated with positive blood culture results. The authors, however, made no distinction between positive blood culture results and true bacteremia.

Surgical ICU patients are reported to be two to six times more likely than medical ICU patients to have bacteremia,[5,21,24] despite the lower incidence of chronic illness in surgical patients. The greater number of procedures and invasive devices used in surgical ICU patients may account for the increased rates of bacteremia. Given the surgical population of patients studied by Darby et al,[21] the incidence of bacteremia in their patients was unexpectedly low. Most of the culture samples were drawn while the patients were receiving antibiotics, and up to one third of the samples were solitary sets. These two factors at least partially account for the low incidence of bacteremia reported in this study, a rate lower than a comparable European study of mostly surgical ICUs with a reported incidence of bacteremia of 5.4 per 100 ICU admissions.[25]

In a review of nosocomial bacteremia in an adult ICU consisting predominately of medical patients, the incidence of bacteremia, during a 5-year observation period (from 1991 to 1995), was 3.7 per 100 ICU admissions.[5] Pseudomonas spp, Enterococcus spp, and coagulase-negative staphylococci were the most frequently isolated organisms, and up to 75% of the bacteremic episodes were attributed to colonized intravascular catheters.

Methodologic differences aside, these findings are surprisingly similar to the previously discussed results by Darby et al.[21] Despite these similarities, the yield of blood cultures in medical ICU patients has

not been well studied, and results from the surgical critical care unit cannot be readily extrapolated to other ICU populations.

Methods to Improve Blood Culture Yield

The overall yield of blood cultures can be affected by several factors (Table 1). Solitary blood cultures, intermittent bacteremia, a low number of colony forming units detectable in blood, antimicrobial properties of blood components, and concurrent antibiotic treatment can all lower the yield of blood cultures. The specific blood collection system used (BACTEC; Becton Dickinson Diagnostic Instruments Systems; Sparks, MD, and DuPont Isolator; Wampole Laboratories; Cranbury, NJ) can play a role in increasing yields in particular clinical settings.[26]

Several authors have addressed the issue of the optimal number of blood cultures needed to detect bacteremia. In their analysis of 500 episodes of septicemia, Weinstein et al[20] noted that 91.5% of all bacteremic episodes were detected by the first blood culture. An additional 7.8% were identified by a second blood culture.[20] For patients with continuous bacteremia (*eg*, endocarditis) in whom one blood culture result was positive, the probability that subsequent culture results would be positive was $> 95\%$. In cases of intermittent bacteremia, approximately 85% of second culture results were positive after an initial positive culture result. Of note, when the initial culture was judged to be contaminated (based on clinical criteria), the probability of a second positive blood culture result was $< 5\%$, and with further testing this decreased to $< 1\%$. When the second culture result was positive, it almost invariably grew a different (contaminating) organism. Based on this and similar studies, for the vast majority of patients there is no evidence that obtaining more than two or three sets of blood cultures (defined as blood cultures of samples drawn from two or three different sites) within a 24-h period improves diagnostic yield. Drawing more than one culture set is useful, however, since obtaining two or three sets can help distinguish true bacteremia from contaminated cultures.[18,19,26–29]

Several technical factors, including skin preparation methods, blood incubation time, type of culture media, and the type of blood collecting system used, can improve the yield of cultures (Table 2). Venipuncture is the preferred method for obtaining blood culture samples. Blood culture samples drawn from intravascular catheters are not optimal, as they can become contaminated with organisms colonizing the hub or the walls of the catheter. If it becomes necessary to obtain culture samples from these catheters, strict aseptic technique should be followed, while all efforts are made to draw a second set of culture samples from a peripheral venipuncture.

Aseptic blood collection techniques and careful processing of cultures in the microbiology laboratory have been shown to decrease the rate of occurrence of skin contaminants.[29,30] One issue of interest is the choice of material used for skin disinfection. None of the commercially available antiseptic products work instantly; a minimum exposure time is required for each product to be effective. While this time varies by agent, it is generally recommended that sufficient time be allowed for the solution to dry prior to venipuncture.[27,31] Materials often used include tincture of iodine, povidone-iodine alone or in combination with isopropyl alcohol, and recently, chlorhexidine. Published studies and recommendations vary in their choices of material for skin disinfection.

In one randomized study,[32] blood culture contamination rates were observed after disinfection of the venipuncture site with either 10% povidone-iodine or 2% iodine tincture. A 70% isopropyl alcohol applicator was used for a 1-min scrub prior to the

Table 1—*Factors Influencing Blood Culture Yield*

Blood barriers
Low number of colony forming units detectable
Intermittent bacteremia
Bactericidal properties of blood components (lysozymes, complement factors, neutrophils, antibodies)
Clinical and laboratory barriers
Volume of blood drawn
Concurrent antibiotic use
Number of blood samples cultured
Timing of blood cultures
Length of incubation of blood cultures
Atmosphere of incubation
Culture media and collecting system used

Table 2—*Guidelines to Improve Blood Culture Yield*

Skin should be adequately disinfected prior to blood culture.
Avoid singular blood culture sets; two or three culture sets (each set consists of aerobic and anaerobic bottles) should be obtained from different venipuncture sites in a 24-h period.
At least 10 mL of blood should be drawn per culture bottle.
Blood culture samples drawn from vascular catheters should be paired with a peripheral blood culture sample to help distinguish contaminants from true pathogens.
Various culture media and collecting systems should be used in accordance with the clinical scenario and with the advice of the microbiology laboratory.
Whenever possible, blood should be drawn prior to initiation of antibiotics. In the presence of antibiotics, drawing culture samples when antibiotic concentrations have reached trough levels may improve yield.

application of either disinfectant, and a 2-min drying time before phlebotomy was recommended for both povidone-iodine and iodine tincture.[32] A total of 3,851 blood cultures were studied; 376 results were positive, of which 120 cultures were contaminated. Compared to povidone-iodine, iodine tincture was responsible for a statistically significant reduction in skin flora contamination (2.4% compared to 3.8% after disinfection with povidone-iodine; odds ratio, 1.6; $p = 0.01$). The difference noted may in part be due to the faster onset of action of tincture of iodine compared to povidone-iodine. The recommended drying time for povidone-iodine to have maximal antiseptic effect is 2 to 3 min. In a busy hospital setting such as the ICU, the nurses or house-officers may not wait for the required skin contact time prior to drawing a blood culture sample, rendering povidone-iodine less effective.

Another randomized controlled trial[33] demonstrated that 0.5% alcoholic chlorhexidine applied to the skin 15 to 30 s prior to venipuncture reduced the incidence of blood culture contamination compared to povidone-iodine applied in a similar manner. Alcoholic chlorhexidine requires less time than povidone-iodine to achieve skin antisepsis (seconds compared to minutes), and this may lead to its greater usefulness in clinical practice. Current evidence suggests that iodine tincture, alone or in combination with isopropyl alcohol, or alcoholic chlorhexidine are both more effective than povidone-iodine in reducing the rates of contamination with skin flora. To date, no direct comparisons have been made between chlorhexidine and tincture of iodine. Nonetheless, the weight of the evidence in the literature advocates the use of some type of a disinfecting agent, and care must be taken to allow adequate time for effective antisepsis prior to venipuncture.

Few studies have evaluated the optimal timing of blood cultures. In clinical conditions with continuous bacteremia, such as endocarditis or septic thrombophlebitis, this issue is probably not very relevant. In cases of intermittent bacteremia, a report[29] from the 1950s that has become the basis for traditional teaching suggests that bacteremia precedes the onset of fever and chills by 1 to 2 h. According to this report, blood culture results are often negative at the time fever occurs. For obvious reasons, drawing blood samples during the 1-h time window prior to fever can be practically impossible. Nonetheless, drawing multiple[2,3] culture sets in a 24-h period has been shown to be sufficient to detect intermittent bacteremia.[20] The ideal interval between blood cultures is not well known, but likely has less impact on the yield than was once thought.[34] In a study of the optimal time interval between blood cultures, Li et al[34] demonstrated that similar yields were obtained when samples were collected simultaneously, within 2 h, or within 24 h of the initial blood culture. In critically ill patients who are hemodynamically unstable, two blood culture sets should be drawn promptly prior to initiation of empiric antibiotic treatment. In less urgent cases, blood can be drawn over a 24-h period. In patients receiving antibiotics, it has been suggested that culture samples drawn close to the time that antibiotic concentrations have reached trough levels may improve yield.[29,35] However, this has not been studied objectively and may not be clinically practical.

The volume of blood drawn is perhaps the most important factor in increasing the sensitivity of blood cultures. Adult patients with clinically significant bacteremia often have a low number of colony-forming units per milliliter of blood (1 to 10 cfu/mL). There is a direct relationship between the volume of blood obtained and the yield of the culture. Various studies reveal that at least 10 mL, but optimally 20 to 30 mL, of blood provide the highest yield and lowest number of false-negative blood culture results. Drawing > 30 mL of blood per culture does little to improve the sensitivity of the blood culture, and contributes to iatrogenic causes of anemia.[26,34,36–39] In a study of blood culture practices at the University of Wisconsin Hospital and Clinics, investigators noted that 15% of all adult blood culture samples were collected in 3.5-mL pediatric blood culture tubes. Five percent of samples collected in the appropriate adult 10-mL tubes contained < 5 mL of blood. The sensitivity for detecting Gram-positive bacteremia with culture samples containing 10 mL of blood was 93%, compared to only 74% when smaller volumes of blood were sampled.[38] A survey of 158 US clinical microbiology laboratory directors revealed comparable results; only 20% of the 71 laboratories responding to the survey reported routinely recording the volume of blood submitted, and up to 88% of these laboratories accepted samples that contained ≤ 5 mL of blood.[38] Given the seemingly widespread practice of obtaining low volume blood samples, educating house-staff, phlebotomists and nurses about the adequate amount of blood needed for culture is a simple measure to increase the yield of blood cultures.

Blood culture yield is also decreased by blood components such as phagocytes, antibodies, and complement factors that are known to have bactericidal activity, impairing the isolation of microorganisms from blood cultures.[20] Use of the anticoagulant sodium polyanetholsulfonate (SPS) 0.025% in blood culture media has been shown to help counteract these bactericidal effects by inhibiting phagocytosis and lysozymal activity.[26,29,40] In addition to having antiphagocytic properties, SPS inactivates aminogly-

cosides. Although it has the potential drawback of inhibiting the growth of fastidious organisms such as *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, and *Neisseria meningitidis*, increasing concentrations of SPS increase the recovery of Gram-negative bacteria.[29,41,42] Virtually all commercially available blood culture bottles and media now use SPS.[41]

Many critically ill patients are on empiric antibiotic treatment at the time blood culture samples are drawn. In one study, up to 65% of blood culture samples were obtained from patients receiving antibiotics.[21] Antibiotic therapy may significantly decrease the yield of blood cultures.[29,43] Recently, blood culture yield in febrile hospitalized patients during 72 h of antibiotic therapy was retrospectively compared to the yield of blood culture samples obtained in the same patients prior to antibiotic administration.[44] Fifty-six of 139 eligible patients (40%) had positive blood culture results prior to antibiotics. Of these, only 26 patients (less than half) continued to have positive culture results within 72 h of antibiotic use. Patients who had *S aureus*, aerobic Gram-negative bacilli, and streptococci isolated from preantibiotic cultures were more likely to have persistently positive blood culture results within 72 h of antibiotic use. Only one patient had a blood culture result during the 72-h study period that was positive for an organism that had not been isolated from her preantibiotic blood cultures. Isolation of *S aureus* from preantibiotic blood cultures and a diagnosis of endocarditis were the only independent predictors of positive blood culture results after antibiotic use. The data from this study suggest that successive blood cultures during the initial 72 h of antibiotic administration rarely yield new and clinically useful information.

The impact of antibiotic use on blood culture yield can be minimized by obtaining an adequate volume of blood for culture. Culturing 10 mL of blood per 100 mL of culture broth dilutes the concentrations of antibiotics and of neutralizing serum bactericidal activity in the cultures.[26] Several manufacturers have marketed blood culture media containing antibiotic-adsorbent resins. Such media include BacT/Alert FAN media (Organon Teknika; Marcy L'etoile, France), a variety of resin-containing BACTEC culture media, and the antimicrobial removal device (ARD; Becton Dickinson Microbiology Systems; Cockeysville, MD) used with manual blood culture systems (*eg*, Septi-Chek; Becton Dickinson Microbiology Systems).[39] Several reports have been published on the use of the antimicrobial removal device, but the results of these studies have been conflicting.[45–47] Routine use of the antimicrobial removal device is generally not recommended; it may be useful in the setting of septic patients who have been receiving antibiotics and have had persistently negative blood culture results after 48 h of incubation.[46]

Most microbiology laboratories use automated blood culture systems, and the nonradiometric BACTEC systems are the most widely used automated systems.[46] No one system currently available can isolate all the organisms that may be present in bacteremic patients. Blood cultures in patients with fungal and mycobacterial infections deserve special mention. Fungi are important nosocomial pathogens, especially in the critical care setting. Risk factors for the development of fungemia include the prolonged use of broad-spectrum antibiotics, the presence of intravascular catheters, the use of parenteral nutrition, and various immunocompromised states. Recovery of fungi in blood cultures is best achieved by lysis-centrifugation systems (DuPont Isolator) rather than conventional blood culture systems. The lysis of RBCs, centrifugation, and inoculation on antibiotic-free solid media increase the yield of microorganisms such as yeast, mycobacteria, filamentous fungi, and Legionella. The DuPont Isolator system also allows for faster recovery of these organisms and quantitation of organisms in blood cultures.

The BACTEC system (and other conventional systems such as BacT/Alert) is superior to the DuPont Isolator system for the isolation of *Streptococcus pneumoniae, Pseudomonas aeruginosa*, anaerobic bacteria, and other Streptococcus species.[39] The use of a combination of BACTEC and DuPont Isolator systems allows for the detection of a broad range of bacterial and fungal infections. However, the regular use of both systems for all patients is neither indicated nor economically feasible. For routine clinical situations, the conventional culture systems are adequate. Lysis-centrifugation systems (*eg*, DuPont Isolator) should be used when there is suspicion of a fungal or mycobacterial infection, and in conjunction with expertise from the infectious disease and microbiology departments. To optimize blood culture yield, each individual microbiology lab should be consulted for information about which of the commercially available conventional systems are readily available and appropriate for the suspected pathogens. A more detailed discussion of blood culture media and systems is beyond the scope of this article, and the reader is referred to excellent reviews of this topic.[27,37,39,48–51]

Contaminant Blood Cultures: Costs and Consequences

The low yield of blood cultures and the large proportion of false-positive results may lead to ex-

tensive diagnostic testing, excessive antibiotic use, and prolonged hospitalization. Studies in unselected hospitalized patients have shown that only 7.5% to 12.4% of all results of blood culture sets are positive; of these, up to 4.9% are considered contaminants.[20,21,52]

Bates et al[8] prospectively studied blood culture results obtained in a single academic center during a 6-month period. The primary end point was resource utilization starting 2 days after blood culture samples were drawn. Lengths of stay, as well as pharmacy, IV antibiotic, microbiology, and total charges, were evaluated. A total of 1,516 blood culture episodes, defined as the 48-h period following initial blood culture, were identified. Of the 219 positive culture results, 104 cultures were considered contaminants, based on clinical judgement. Blood cultures from samples drawn through intravascular catheters were contaminated 6% of the time, compared to 3% drawn from peripheral venipunctures. A single blood culture set was drawn in 22% of episodes; in 55% of culture samples drawn from intravascular catheters, paired peripheral samples to confirm the presence of true bacteremia were not obtained. Contaminated blood cultures were also more likely to occur in uncooperative patients with altered mental status, in whom it was often difficult to achieve and maintain sterile technique during venipuncture.

In the same study, after controlling for severity of illness and diagnosis, contaminated blood cultures increased unnecessary IV antibiotic charges by 39%. By escalating the number of repeat blood cultures, contaminated cultures also led to 80% higher microbiology laboratory charges. There was a trend toward increased length of stay, but this was not statistically significant. Although this study has several limitations and results may not be readily generalized, the authors highlight the fact that contaminated blood cultures comprise a significant proportion of all positive blood culture results, often generating costs that far exceed the costs of the test itself.[8]

There is a paucity of data on the incidence and costs of contaminants in the critical care setting. Schwenzer and colleagues[17] studied blood cultures from a surgical ICU over a 2-year period; of 1,411 blood cultures, there were 122 positive culture results, and 51 of these were considered contaminants. Coagulase-negative staphylococci were considered true pathogens only if isolated from both a central line and peripheral venipuncture, from two peripheral blood culture sets, or from patients who were clinically septic and had a single positive culture result from a central venous catheter. Most other skin organisms were considered contaminants. No cost data were provided in this study, and no good estimates exist in current literature. However, it is likely that the costs and consequences of contaminant blood cultures parallel or exceed estimates available for unselected hospital admissions. Differentiating contaminants from true pathogens is often difficult. In one of the earlier studies on this topic, MacGregor and Beaty[19] determined that pneumococci, group A Streptococci, Enterobacteraceae, Bacteriodes, Candida, and Haemophilus spp were true pathogens in their series of patients. Diphtheroids, nonhemolytic streptococci, and Bacillus spp were usually contaminants. Polymicrobial infections occurred in injection drug users or in patients who had leukemia or were receiving chemotherapy. In this study, clinical criteria alone were used to determine whether a positive blood culture result represented true bacteremia or contamination. When two or more blood culture samples were drawn, 69% of patients with a clinical course suggestive of bacteremia had repeatedly positive culture results. This number may be deceptively low, since paired blood culture samples were not drawn, and subsequent culture samples were often drawn while patients were receiving antibiotics. In contrast, only 11% of patients classified as having a contaminated blood culture had positive blood culture results on repeated testing, and often different organisms were isolated. This study highlights the importance of drawing multiple (*ie*, two or more) blood culture samples as an aid to differentiating between true bacteremia and contaminated cultures.

While there are no standardized criteria, several general observations can help guide the clinician in determining the clinical significance of positive blood culture results (Table 3). False-positive culture results tend to require prolonged incubation periods before isolation of an organism.[18,19] Contaminating

Table 3—*True Bacteremia vs Contaminated Blood Cultures*

Suggestive of true bacteremia
Growth of virulent organisms such as *S pneumoniae,* Klebsiella species, pseudomonas species, *S aureus,* and Enterobacteriaceae and Candida species.
Presence of predisposing risk factors such as immunocompromised states, prostheses, indwelling lines.
Recovery of the same organism from multiple sites.
Suggestive of contaminated culture
Prolonged incubation period before growth of organism.
Lack of reproducibility in subsequent cultures.
Culture yields multiple organisms.*
Patient's clinical condition is not suggestive of sepsis.
Growth of skin flora, *eg,* coagulase-negative staphylococci,† diphtheroids, and Bacillus species.

*Except in immunocompromised and neutropenic patients or in presence of intra-abdominal infections.

†Up to 15% of coagulase-negative staphylococci isolates are true pathogens; this is more likely in the presence of indwelling catheters.

organisms often do not grow from multiple consecutive blood culture sets. Contamination is usually due to skin flora such as diphtheroids and Bacillus species, whereas Enterobacteriaceae spp, Pseudomonas spp, *S pneumoniae*, *S aureus*, and *Candida albicans* are rarely contaminants. Coagulase-negative staphylococci present a unique problem; although the majority of isolates are contaminants, 6 to 15% are true pathogens. In addition, coagulase-negative staphylococci are the most common cause of catheter-related infections.[53] The significance of coagulase-negative staphylococcus isolates should be judged on the basis of a patient's clinical condition and laboratory data.[18,19,39,54] The recovery of multiple organisms also suggests contamination rather than true bacteremia, except in immunosuppressed or neutropenic patients, and in critically ill patients with intravascular catheters or clinical findings suggesting intra-abdominal infection.[55]

Central venous catheters present a particular challenge to the physician trying to distinguish between true bacteremia and contaminated blood cultures. On a yearly basis, an estimated 850,000 catheters become colonized, resulting in 50,000 cases of catheter-related bacteremia.[56] The body of literature on the diagnosis and management of central catheter infections is rapidly growing. The multiplicity of methods used in diagnosing such infections and the variability of results are at times confusing. Identifying IV catheters as a source of bacteremia is often a diagnosis of exclusion, as usually there are no focal findings at the catheter insertion site. Positive blood culture results obtained from intravascular catheters may reflect colonization, contamination with skin flora, or true catheter-related bacteremia. In an attempt to avoid unnecessary removal of catheters, quantitative blood cultures have been used to diagnose catheter-related bacteremia. Paired samples of blood are obtained from the catheter hub and from a peripheral venipuncture site for quantitative culture. A fivefold to 10-fold increase in the colony count obtained from the catheter sample compared to the peripheral blood specimen is considered indicative of catheter-related bacteremia.[53,57] Quantitative blood cultures are not readily available in all hospitals, however, and their use is not without controversy.[58]

The continuous-monitoring blood culture systems currently available (*eg*, BacT/Alert) have thus been used instead to determine the differential time to positivity of blood culture samples obtained from central venous lines compared to peripheral vein samples. Blot et al[59] noted that earlier positive culture results from central catheters were predictive of catheter-related infections. In their population of oncology patients with long-term (> 30 days) and often tunneled catheters, this method was highly sensitive (96.4%) and specific (100%) when the differential was > 120 min.[59,60] Rijnders and colleagues[61] prospectively evaluated this technique in 100 critically ill patients with short-term intravascular catheters. These investigators, however, were unable to demonstrate a significant difference in differential time to positivity between patients with catheter-related bacteremia and patients with other causes of bacteremia.[61] Due to the small number of central catheter infections in this study, strong conclusions cannot be made. The validity of this method for noncancer patients and in the setting of multiple short-term central catheters requires further study prior to recommendations for its routine use as an alternative to quantitative blood cultures.

In general, to distinguish between contaminated cultures and true episodes of bacteremia, clinicians must consider any positive blood culture result in its proper clinical context. A positive blood culture result is more likely a true-positive result when the pretest probability of bacteremia is high, as in a patient with predisposing risk factors and a clinical course suggestive of sepsis.

Predictors of Bacteremia

Theoretically, it may be possible to decrease the number of false-positive culture results by diminishing the number of blood culture samples drawn in patients who are at low risk for bacteremia. Prediction rules to determine the pretest probability of bacteremia in patients admitted to the hospital have been developed.[11,12,14,15,17,62–65] These rules have been limited in value, however. They are often retrospective in nature, analyze a subset of patients, lack external validity, and are not readily generalized to the critically ill population.

In an effort to determine the probability of bacteremia in hospitalized patients, Bates et al[11] performed a prospective observational study of 1,007 blood culture episodes (defined as blood culture samples drawn in a 48-h time period) in a tertiary care setting. Factors correlating with true bacteremia included major comorbidity, body temperature ≥ 38.3°C, shaking chills, a clinical examination significant for an acute abdomen, or IV drug use. True bacteremia was also associated with the presence of an underlying disease considered to be "rapidly" fatal in 1 month (*eg*, acute untreated leukemia) or "ultimately" fatal within 5 years (*eg*, metastatic colon cancer). Coma, multiple trauma or burns, cardiopulmonary arrest within 24 h of the study period, ARDS, liver failure, bowel perforation, and severe pancreatitis were considered major comorbidities.

Points were assigned for each identified risk factor. Patients with three or more risk factors or with 10 points were determined to be at high risk for bacteremia and had a 14% probability of true bacteremia. This is in contrast to the low-risk group with no identifiable risk factors, who had a 2% likelihood of true bacteremia on blood culture results.[11] Unfortunately, this prediction model cannot be generalized to the critically ill population of patients, most of whom already fall into the high-risk category defined by this study.

Traditionally, the presence of fever in the ICU patient has been the impetus for extensive imaging and for drawing frequent blood culture samples to rule out bacteremia. Although infectious causes of fever lead to considerable morbidity and mortality and warrant further investigation, noninfectious etiologies of fever should also be considered (Table 4). When considered in the context of other clinical and laboratory clues, the presence of fever may increase the suspicion of bacteremia. However, fever is not a reliable predictor of bacteremia in the ICU population. Ironically, a proportion of bacteremic patients are afebrile, making the task of predicting sepsis and bacteremia in the ICU a difficult one. In one of the few studies looking at predictors of bacteremia in the critically ill, Schwenzer et al[17] retrospectively compared 24 surgical ICU patients who had one or more positive blood culture results to 48 control patients with negative culture results, matching for admitting diagnosis, procedures, severity of illness on admission, and age. The decision to obtain blood culture samples was left to the discretion of the attending physician, but often was determined clinically in the presence of body temperature of $\geq 38.5°C$, hypothermia, hypotension, leukocytosis, and changes in mental status. Clinical data were reviewed 5 days before and after initial blood culture samples were drawn. There was a 5% true-positive rate. Patients with bacteremia were three times more likely to die than matched control subjects. This study, however, was unable to identify any clinical predictors of bacteremia in this population of surgical ICU patients. In particular, there was no correlation between the presence of fever, hypotension, and leukocytosis (factors that often raise the suspicion of nosocomial infection in the ICU) and bacteremia.

Table 4—*Noninfectious Etiology of Fever in the ICU*

Skin
Hematoma
IM injections
Burns
CNS
Hemorrhage (intracerebral, subdural, subarachnoid)
Infarction
Seizures
Cardiovascular
Myocardial infarction
Dressler syndrome
Aortic dissection
Pericarditis
Pulmonary
Pulmonary embolus
Aspiration or chemical pneumonitis
Fat embolus
ARDS
GI
Pancreatitis
Acalculous cholecystitis
Inflammatory bowel disease
Ischemic colitis
Nonviral hepatitis
Retroperitoneal or GI hemorrhage
Metabolic/endocrinologic
Alcohol or other drug withdrawal
Hyperthyroidism
Adrenal insufficiency
Malignant hyperthermia
Heat stroke
Rheumatologic/inflammatory
Collagen vascular disease
Gout/pseudogout
Vasculitis
Miscellaneous
Drug fever
Neoplasm
Deep venous thrombosis

Even less is known about clinical predictors of bacteremia in medical ICU patients, many of whom have several comorbidities and are immunocompromised. Studies in this area are made difficult by the heterogeneous nature of ICU patients, the lack of agreement on diagnosis of certain conditions (*eg*, ventilator-associated pneumonias), and the presence of clinical states that mimic sepsis. Regardless, the considerable impact of nosocomial infections and bacteremia necessitates the early diagnosis and treatment of these infections.

Conclusion

Sepsis is an important cause of morbidity and mortality in the critical care unit. Bacteremia in critically ill patients has an average attributable mortality of 26%,[2] but clinical parameters are often not reliable predictors of bacteremia. As the standard for diagnosing bacteremia, blood cultures have low yield. The volume of blood drawn in adult patients is the single most important factor improving blood culture sensitivity, and at least 10 mL, but optimally 20 mL, of blood should be drawn. Two sets of culture samples drawn from separate venipuncture sites will help the clinician distinguish contaminants from true-positive results. Blood culture sam-

ples drawn from intravascular devices should be avoided, or if necessary paired with a peripheral venipuncture. Although fever is not a specific predictor of bacteremia, its presence often triggers an elaborate diagnostic workup. Blood cultures remain a valuable diagnostic tool. Every effort should be made to improve the yield of this diagnostic modality, and results obtained should be interpreted in light of clinical and other laboratory data. Once bacteremia is identified, repeated cultures with each temperature elevation, especially in patients who are clinically unchanged, are unnecessary. The judicious use of cultures, while paying attention to factors that improve blood culture yield and decrease contamination rates, will improve the utility of blood cultures as diagnostic tools in critically ill patients.

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