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Blood Cultures: the Importance of Meeting Pre-Analytical Requirements in Reducing Contamination, Optimizing Sensitivity of Detection, and Clinical Relevance

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Abstract

The primary goal of the clinical microbiology laboratory is to provide reliable, timely, and clinically relevant diagnostic test results. Blood cultures are one of the most important specimens managed by the clinical microbiology laboratory and are the primary and most sensitive method for diagnosing blood stream infections (bacteremia, fungemia, and sepsis), in addition to influencing appropriate antimicrobial therapy. Of the three phases of laboratory testing, pre-analytical, analytical, and post-analytical, the former is the most challenging for the clinical microbiology laboratory to control. The primary pre-analytical factors that significantly influence the sensitivity, interpretation, and clinical relevance of blood cultures are (i) skin antisepsis, (ii) blood volume, (iii) number of blood culture specimens collected, (iv) timing of blood culture collection, and (v) delays in incubation time. This overview focuses on these pre-analytical factors and the potential impact on blood culture results, which are essential for promoting safe, timely, effective, and efficient care for patients with serious infections, in addition to affecting health care expenses.

Introduction

Bloodstream infections (BSIs) are a major cause of morbidity and mortality in hospitalized patients (1-3). Nearly 200,000 episodes of BSIs occur in the United States each year, with an incidence of approximately 10 per 1,000 hospital admissions (4-7) and mortality rates of 14% to 37%, with the highest incidence (35%) occurring in intensive care patients (8-11). No definitive or evidence-based guidelines have been established or published that specify when blood cultures should be collected. It is generally accepted that blood cultures should be obtained when patients exhibit fever, chills, leukocytosis, focal infections, or signs of sepsis; in cases of suspected endocarditis; or prior to initiating antimicrobial therapy (3). Driven by the high mortality associated with bacteremia, the dangers of undertreating some infections, or concern with using inappropriate antibiotics, physicians tend to order blood cultures liberally, which most likely accounts for the low rate (4% to 7%) of clinically significant blood cultures (3).

Skin Antisepsis

Contaminated (false-positive) blood cultures, defined by the National Healthcare Safety Network as the recovery of commensal skin flora (coagulase-negative staphylococci, *Aerococcus*, *Micrococcus*, *Propionibacterium* spp., *Bacillus* spp. [not *B. anthracis*], *Corynebacterium* spp. [diphtheroids], and alpha-hemolytic streptococci) from a single blood culture, is regarded as a health care quality issue (12). The average adult inpatient contamination rate within U.S. hospitals is 2.9%, but rates as high as 50% have been reported for some institutions (13). The consequences of contaminated blood cultures include increased hospital length of stay (range, 3 to 3.5 days); unnecessary administration of antimicrobial

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agents, which increase the patient's risk for complications, including alteration of the microbiota; increased rates of colonization with multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE); increased rates of *Clostridium difficile* infection; allergic reactions; increased diagnostic testing; and increased health care costs, ranging from $1,000 to $8,750 per false-positive culture (13-15). Many studies have shown that implementing standardized practices for blood culture collection by a dedicated, laboratory-based phlebotomy team or, in some institutions, the use of sterile blood culture collection kits has resulted in a significant reduction in contamination and net savings to the institution (16-19).

Of the methods used for obtaining blood for culture, the venipuncture approach remains the method of choice; obtaining blood for culture from indwelling, intravascular-access devices (PICC lines, Hickman, central lines, etc.) is discouraged due to their association with higher contamination rates than those collected via venipuncture (20). Furthermore, arterial blood cultures are not recommended because the diagnostic yield is equivalent to or no higher than blood cultures collected by venipuncture (20). Because the patient's skin is the most likely source of contamination with commensal organisms, strict adherence to careful technique, including correct preparation of the venipuncture site prior to collecting blood for culture, is a critical factor in reducing contamination (false positives). The key steps in obtaining blood for culture and reducing contamination are as follows: (i) apply a tourniquet with the ends facing away from the vein puncture site, (ii) palpate the vein, (iii) disinfect the venipuncture site, and (iv) disinfect the blood culture bottle tops (rubber diaphragm) or, if collecting from an intravascular device, the catheter hub/port diaphragm.

Inadequate skin antisepsis is the leading cause of blood culture contamination, combined with inadequate drying time of the disinfectant, the technique used to disinfect the venipuncture site, and touching the site following application of the disinfectant (18). There is a lack of consensus regarding which antisepsis is best for disinfecting the venipuncture site. The three most commonly used agents are (i) iodine tincture (2% iodine and 2% sodium iodide diluted in 50% ethanol), (ii) 10% povidone iodine aqueous solution, and (iii) 2% chlorhexidine gluconate/70% isopropyl alcohol. Of these, chlorhexidine gluconate is generally accepted as the preferred agent. However, in a recent systematic review and meta-analysis, the choice of antiseptic agent does not directly impact contamination rates, but rather, the technique used to disinfect the venipuncture site (18,20), in addition to having a dedicated, well-trained phlebotomy team responsible for blood culture specimen collection (14).

Since no clear difference has been noted between iodine-containing and chlorhexidine-containing disinfectants, the efficacy of each was enhanced with the inclusion of alcohol. It is recommended that an alcohol-based disinfectant consist of 70% isopropyl alcohol or ethanol, followed by chlorhexidine, with a drying time of 30 s, or a 1-min drying time for tincture of iodine; betadine preparations are not recommended due to the length of the drying time (1.5 to 2 min) needed to be effective (21). The rubber diaphragm of blood culture bottles, as well as catheter access sites, are not sterile and should also be vigorously disinfected with 70% ethanol or isopropyl alcohol. The overall blood culture contamination rate should not exceed 3% (20, 21). Application of the proper skin preparation disinfectant is very important, but of equal importance, and perhaps more, is the technique that is employed to apply the disinfectant. It is generally accepted that disinfectants should be applied to the venipuncture site in a concentric (beginning at the center of the vein and moving in an outward direction), or "bull's eye," fashion. Of the two primary venipuncture site preparation methods (concentric versus back-and forth friction), the back-and-forth friction method, in which the disinfectant is applied to the center of the site, followed by a back-and-forth outward motion until an area of 2 to 3 inches has been scrubbed, has gained in popularity. The advantage of this method is the cleansing of the top 5 dermal layers of the skin (22). Additionally, scrubbing with this method removes a greater part of the bacterial load that resides in the upper dermal layers of the skin, where the majority of commensal organisms are located. Evidence from a meta-analysis established that of the two skin-cleansing techniques (concentric and back-and-forth friction), chlorhexidine gluconate combined with alcohol and applied with the back-and-forth friction method was the most effective in reducing blood culture contamination (22). Additional evidence-based studies are needed to clearly establish "best practice" guidelines for venipuncture site preparation.

As more and more patients have indwelling intravascular devices, the issue of intravascular access device BSIs has become a major challenge for nursing, clinicians, and the microbiology laboratory. Clinicians and nurses believe that drawing blood for culture through intravascular devices increases the likelihood of determining the cause of bacteremia and sepsis, because the catheter is regarded as the most likely source of the infection; in addition, phlebotomy is difficult and painful for patients in intensive care who are subjected to multiple intravascular accesses or have coagulation disorders (22). Some studies have shown that the rate of contamination when blood is collected through an intravascular device is not significantly higher than when it is collected blood by venipuncture (22). Regardless, the key to reducing contamination when drawing blood for culture from an intravascular device is to ensure that the lumen or catheter diaphragm is thoroughly disinfected with 70% isopropyl alcohol or ethanol before inserting the needle to collect the blood. From the perspective of interpreting the source of the bacteremia or fungemia, particular attention should be given to "time to positivity," defined as the time between collection and detection as positive by an automated continuous-monitoring blood culture detection instrument. Generally, if a culture drawn through a line or lumen is positive 90 to 120 min before a culture that is collected from another site (venipuncture, catheter, or lumen), the results suggest that the culture with the earlier positivity contains a higher organism burden and represents the source of the infection (22). This does not alleviate the responsibility of the clinician or nurse to practice good catheter