

Diagnosis of Catheter-Related Bloodstream Infection: Conservative Techniques

Josefina Liñares

Department of Microbiology, Hospital Universitario de Bellvitge, Barcelona, Spain

(See the article by Bouza et al. on pages 820–6)

Intravascular catheters have been an important technological advance for modern medicine. However, the use of intravascular catheters is associated with infection, which is a potentially life-threatening complication. Catheter-related bloodstream infection (CR-BSI) is the most serious infection associated with catheter use, and it is responsible for significant medical costs. It is estimated that ~250,000 episodes of CR-BSI occur annually in hospitals in the United States, with an estimated attributable mortality of 12%–25%. In addition, it is well recognized that CR-BSI increases the duration of hospital stay and medical costs per patient. One-half of all nosocomial bloodstream infections in US hospitals occur in patients receiving critical care, and CR-BSI accounts for one-third of these infections [1–3].

There are 4 potential sources of catheter colonization and catheter-related infections: the skin insertion site, the catheter hub, hematogenous seeding of the catheter tip from a distant site of infection,

and infusate contamination [4–6]. For decades, it has been accepted that skin colonization and the progression of microorganisms on the external surface of the catheter are the most common origins of catheter colonization and infection [4, 7, 8].

However, the relevance of the endoluminal route in the pathogenesis of CR-BSI was recognized during the mid-1980s by Sitges-Serra and colleagues [5, 6, 9]. The authors demonstrated that 70% of CR-BSIs in patients with central venous catheters for parenteral nutrition were caused by hub contamination [6]. Salzman et al. [10] reported that 54% of CR-BSI episodes in neonates were preceded by or coincided with contamination of the hub. The endoluminal route is the dominant mechanism for colonization of long-term catheters, whereas recently inserted catheters are most commonly colonized by an extraluminal route [11]. Hub contamination is more often associated with bacteremia than with skin colonization [5, 6, 9–12].

Clinical findings are unreliable for establishing a diagnosis of CR-BSI, because no characteristic clinical features of CR-BSI exist to distinguish this infection from infections arising from other body sites. Conventional methods of diagnosing CR-BSI generally require that the catheter be removed and cultured with quantitative or semiquantitative methods. However,

>80% of catheters withdrawn because of clinical suspicion of CR-BSI are removed unnecessarily, because the culture results are negative [1]. In addition, the removal of a central venous catheter may be undesirable because of limited vascular access, and there could be serious complications and risks associated with reinsertion. Consequently, a number of diagnostic techniques that do not require catheter removal have been developed to diagnose CR-BSI. Conservative methods to assess catheter-tip colonization or CR-BSI are an important advance and include paired quantitative blood cultures, differential time to positivity, superficial cultures of skin surrounding the portal of entry and catheter hubs, and Gram staining and the acridine orange leukocyte cytospin test [13–21].

The study by Bouza et al. [22] in this issue of *Clinical Infectious Diseases* prospectively compares 3 techniques (paired quantitative blood cultures, differential time to positivity, and superficial cultures) for the diagnosis of CR-BSI without catheter withdrawal in adult patients without neutropenia who had short-term central venous catheters and were admitted to intensive care units. The authors studied 204 episodes of suspected CR-BSI, and 28 of the episodes were confirmed to be CR-BSI. The reference standard for the evaluation of the 3 conservative methods for diagnosis of CR-BSI was paired quanti-

Received 3 December 2006; accepted 4 December 2006; electronically published 6 February 2007.

Reprints or correspondence: Dr. Josefina Liñares, Servicio de Microbiología, Hospital de Bellvitge, 08907 L'Hospitalet de Llobregat, Barcelona, Spain (fina.linaires@csb.scs.es).

Clinical Infectious Diseases 2007;44:827–9

© 2007 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2007/4406-0011\$15.00

DOI: 10.1086/511885

tative blood cultures with positive results (colony count ratio of $>5:1$) and/or conventional cultures of peripheral blood and semiquantitative catheter-tip culture positive for the same microorganism (≥ 15 colony-forming units).

Wing et al. [23] were the first investigators to use paired quantitative blood cultures to diagnose CR-BSI. Other authors demonstrated that a 5- to 10-times-greater colony count in blood obtained through the intravascular catheter than in blood obtained through a peripheral vein is considered to be indicative of CR-BSI [13–16]. Multiple studies have since demonstrated the accuracy of the quantitative methods, and paired quantitative blood culture methods are now regarded as the reference standard for the diagnosis of CR-BSI if catheter removal is undesirable [13–16, 24]. In a recent meta-analysis, Safdar et al. [24] evaluated 8 methods for the diagnosis of CR-BSI and concluded that, among the techniques studied, paired quantitative blood culture was the most accurate test (sensitivity, 0.87 [95% CI, 0.83–0.91]; specificity, 0.98 [95% CI, 0.97–0.99]). The data from Bouza et al. [22] are consistent with this meta-analysis. They reported that paired quantitative blood cultures with a quotient of ≥ 5 represented the best specificity (97.7%) in the diagnosis of CR-BSI and had a sensitivity of 71.4%, a positive predictive value of 83.3%, a negative predictive value of 95.6%, and an accuracy of 94.1%.

However, paired quantitative blood cultures are not routinely used in clinical practice because of their cost and complexity. Blot and colleagues [17, 18], by using a continuous blood culture-monitoring system, have described a new method that is based on differential time to positivity of qualitative blood cultures drawn simultaneously from both a catheter hub and a peripheral vein. The authors found that cultures of catheter-drawn blood that yielded positive results ≥ 120 min earlier than cultures of peripheral blood were accurate in detecting

CR-BSI (specificity, 91%; sensitivity, 94%). Findings by other investigators have shown lower sensitivities and specificities of differential time to positivity than those found by Blot and colleagues [17, 18]. Raad et al. [19] reported sensitivity and specificity of 81% and 92%, respectively, for short-term catheters and 93% and 75%, respectively, for long-term catheters. Seifert et al. [20] found a sensitivity of 82%, a specificity of 88%, a positive predictive value of 75%, and a negative predictive value of 92%. The results published in this issue by Bouza et al. [22] (sensitivity, 96.4%; specificity, 90.3%; positive predictive value, 61.4%; negative predictive value, 99.4%; and accuracy, 91.2%) are comparable to those reported by Blot and colleagues [17, 18].

Because many laboratories now use automated continuous blood culture-monitoring systems, they will be able to use these systems for the diagnosis of CR-BSI by the differential time to positivity method. This technique showed acceptable sensitivity (0.85; 95% CI, 0.78–0.92) and specificity (0.81; 95% CI, 0.75–0.87) in the meta-analysis study of Safdar et al. [24]. This method is easier to perform and is less costly than the paired quantitative blood cultures method.

However, the major disadvantage of culture of blood collected through a central venous catheter for the diagnosis of CR-BSI is a higher rate of contamination, compared with that for culture of blood obtained through a peripheral venipuncture [25]. Clinical and cost implications of false-positive results of cultures of blood obtained through catheters have not yet been well evaluated [26].

The evaluation of conservative studies of skin insertion site and catheter hub cultures for the diagnosis of CR-BSI is often difficult because of methodological differences among the studies and the wide range of cutoff values for positivity. Fan et al. [27] verified that, in catheter sepsis, the positive predictive value of skin culture combined with hub culture was 44%, whereas the negative predictive

value was 93%. Cercenado et al. [8] studied skin and hub cultures and found their sensitivity and specificity to be 96% and 71%, respectively. The most important finding of these studies of skin and hub cultures is that such cultures have a high negative predictive value (93%–99%).

Although the paired quantitative blood cultures and the differential time to positivity methods have excellent sensitivity and specificity, the contribution of the study by Bouza et al. [22] is to demonstrate that the surveillance skin and hub cultures performed well for diagnosis of CR-BSI (sensitivity, 78.6%; specificity, 92.0%; positive predictive value, 61.1%; negative predictive value, 96.4%) in adult patients with short-term catheters who were admitted to intensive care units. The authors did not find differences in accuracy between the 3 techniques that they evaluated.

A possible limitation of the study by Bouza et al. [22] is that, as part of the reference standard definition of CR-BSI, the authors used catheter-tip culture performed according to the roll-plate semiquantitative method [7], and microorganisms that colonized the internal lumen of the catheter could be not recovered. However, these authors have previously demonstrated that quantitative techniques of sonication or vortexing were not superior to the semiquantitative method [28].

Bouza et al. [22] recommend a realistic approach for routine diagnosis of CR-BSI in clinical microbiology laboratories by means of the combination of semiquantitative superficial cultures and conventional peripheral blood cultures. These methods are easy to perform and low in cost. In addition, if Gram staining of swabs of the skin insertion site and the inner surface of the hub is performed, this could provide a rapid and inexpensive conservative method for the diagnosis of CR-BSI. Negative results of Gram staining and culture of both superficial swabs could practically rule out the catheter as the source of infection, thereby avoiding many unnecessary catheter removals. Further

studies of this method for the diagnosis of CR-BSI, including Gram staining and semiquantitative cultures of hubs and skin insertion sites, are needed. Nevertheless, in cases in which CR-BSI is suspected, a prudent attitude must be taken, because a small percentage of CR-BSIs due to hematogenous seeding yield superficial cultures with negative results.

Acknowledgments

Potential conflicts of interest. J.L.: no conflicts

References

- Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249–72.
- O'Grady N P, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2002;30:476–89.
- Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;39:309–17.
- Maki DG. Pathogenesis, prevention and management of infectious due to intravascular devices used for infusion therapy. In: Bisno AL, Waldvogel F, eds. *Infections associated with indwelling medical devices*. Washington, DC: American Society for Microbiology, 1989: 161–77.
- Sitges-Serra A, Puig P, Liñares J, et al. Hub colonization as the initial step in an outbreak of catheter-related sepsis due to coagulase negative staphylococci during parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1984;8: 668–72.
- Liñares J, Sitges-Serra A, Garau J, Perez JL, Martín R. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. *J Clin Microbiol* 1985;21:357–60.
- Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med* 1977;296:1305–9.
- Cercenado E, Ena J, Rodriguez-Creixems M, Romero I, Bouza E. A conservative procedure for the diagnosis of catheter-related infections. *Arch Intern Med* 1990;150:1417–20.
- Sitges-Serra A, Liñares J, Garau J. Catheter sepsis: the clue is the hub. *Surgery* 1985;97: 355–7.
- Salzman MB, Isenberg HD, Shapiro JF, Lipsitz PJ, Rubin LG. A prospective study of the catheter hub as the portal of entry for microorganisms causing catheter-related sepsis in neonates. *J Infect Dis* 1993;167:487–90.
- Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. *J Infect Dis* 1993;168:400–7.
- Salzman MB, Rubin LG. Relevance of the catheter hub as a portal for microorganisms causing catheter-related bloodstream infections. *Nutrition* 1997;13(4 Suppl):15S–7S.
- Mosca R, Curtas S, Forbes B, Meguid MM. The benefits of Isolator cultures in the management of suspected catheter sepsis. *Surgery* 1987;102:718–23.
- Flynn PM, Shenep JL, Barrett FF. Differential quantitation with a commercial blood culture tube for diagnosis of catheter-related infection. *J Clin Microbiol* 1988;26:1045–6.
- Capdevila JA, Planes AM, Palomar M, et al. Value of differential quantitative blood cultures in the diagnosis of catheter-related sepsis. *Eur J Clin Microbiol Infect Dis* 1992;11: 403–7.
- Quilici N, Audibert G, Conroy MC, et al. Differential quantitative blood cultures in the diagnosis of catheter-related sepsis in intensive care units. *Clin Infect Dis* 1997;25:1066–70.
- Blot F, Schmidt E, Nitenberg G, et al. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. *J Clin Microbiol* 1998;36: 105–9.
- Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. *Lancet* 1999;354:1071–7.
- Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med* 2004;140:18–25.
- Seifert H, Cornely O, Seggewiss K, et al. Bloodstream infection in neutropenic cancer patients related to short-term nontunneled catheters determined by quantitative blood cultures, differential time to positivity, and molecular epidemiological typing with pulsed-field gel electrophoresis. *J Clin Microbiol* 2003;41:118–23.
- Krause R, Auner HW, Gorkiewicz G, et al. Detection of catheter-related bloodstream infections by the differential-time-to-positivity method and gram stain-acridine orange leukocyte cytospin test in neutropenic patients after hematopoietic stem cell transplantation. *J Clin Microbiol* 2004;42:4835–7.
- Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C, Muñoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. *Clin Infect Dis* 2007;44:820–6 (in this issue).
- Wing EJ, Norden CW, Shadduck RK, Winkelstein A. Use of quantitative bacteriologic techniques to diagnose catheter-related sepsis. *Arch Intern Med* 1979;139:482–3.
- Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. *Ann Intern Med* 2005;142:451–66.
- DesJardin JA, Falagas ME, Ruthazer R, et al. Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. *Ann Intern Med* 1999;131:641–7.
- Barton T, Mizuta M, Fishman N. Costs of false-positive cultures from central catheters. *Ann Intern Med* 2004;141:162.
- Fan ST, Teoh-Chan CH, Lau KF, Chu KW, Kwan AK, Wong KK. Predictive value of surveillance skin and hub cultures in central venous catheters sepsis. *J Hosp Infect* 1988;12: 191–8.
- Bouza E, Alvarado N, Alcalá L, et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. *Clin Infect Dis* 2005;40:1096–100.