

A Randomized and Prospective Study of 3 Procedures for the Diagnosis of Catheter-Related Bloodstream Infection without Catheter Withdrawal

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(See the editorial commentary by Liñares on pages 827–9)

Background. Suspicion of catheter-related bloodstream infection (CR-BSI) leads frequently to unnecessary catheter withdrawals, and many catheter-tip cultures yield negative results. The objective of this study was to compare the yield of 3 microbiological procedures to assess CR-BSI without catheter withdrawal.

Methods. The study was prospectively performed in a group of patients without neutropenia or blood disorders who were admitted to the intensive care unit during a 37-month period with sepsis suspected on clinical grounds and who had central venous catheters inserted for >48 h. The microbiological procedures compared were semi-quantitative cultures from hub and skin (superficial), differential quantitative blood cultures, and differential time to positivity between cultures of blood obtained from catheter hubs and peripheral blood.

Results. Of the 204 episodes of suspected CR-BSI included in the study, 28 were confirmed to be CR-BSI. We obtained the following results for sensitivity, specificity, positive and negative predictive values, and accuracy: superficial cultures, 78.6%, 92.0%, 61.1%, 96.4%, and 90.2%, respectively; differential quantitative blood cultures, 71.4%, 97.7%, 83.3%, 95.6%, and 94.1%, respectively; and differential time to positivity, 96.4%, 90.3%, 61.4%, 99.4%, and 91.2%, respectively.

Conclusions. CR-BSI can be assessed without catheter withdrawal in patients without neutropenia or blood disorders who have catheters inserted for a short time and are hospitalized in the intensive care unit. Convenience, use of resources, and expertise should determine the technique of choice in different medical contexts. Because of ease of performance, low cost, and wide availability, we recommend combining semiquantitative superficial cultures and peripheral vein blood cultures to screen for CR-BSI, leaving differential quantitative blood cultures as a confirmatory and more specific technique.

Catheter-related bloodstream infections (CR-BSIs) are the leading cause of nosocomially acquired sepsis and contribute significantly to in-hospital morbidity and mortality [1–6]. Confirmation of CR-BSI requires identification of microorganisms recovered from blood and catheter tips. Regrettably, only 15%–25% of the central venous catheter tips that reach the microbiology laboratory turn out to be culture-positive, thereby confirming CR-BSI. Furthermore, not all CR-BSIs require

the catheter to be withdrawn; therefore, diagnosis of CR-BSI by conservative methods (without catheter withdrawal) is highly convenient [7–9].

Conservative procedures to assess catheter-tip colonization or CR-BSI include superficial cultures (semi-quantitative cultures of skin surrounding the portal of entry and catheter hubs), differential quantitative blood cultures (comparing colony counts for peripheral blood samples with colony counts for blood samples from catheter hubs), and, more recently, differential time to positivity (comparing time to positivity between cultures of blood samples obtained simultaneously from peripheral veins and from catheter hubs) [1, 7–12]. The yield of some of these procedures has been prospectively compared only for patients with blood disorders who have long-term catheter use [13]. Our study is the first to prospectively compare 3 different conservative procedures for the diagnosis of suspected CR-BSI in pa-

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tients without blood disorders or neutropenia who have short-term catheter use and are admitted to general intensive care units.

PATIENTS AND METHODS

Patients. Our study was carried out between September 2002 and September 2005 in a cohort of adult patients without blood disorders and without neutropenia who had short-term catheter use and who were admitted to the intensive care unit at our institution (Hospital General Universitario "Gregorio Marañón," Madrid, Spain). Patients with clinical suspicion of sepsis and central venous catheters inserted for >48 h were included in the study. The study was approved by our ethics committee.

A full study included a 3-cm sample of skin swabbing around the insertion site and an alginate swab sample of each of the catheter hubs for semiquantitative culture. The study also included samples from the hub for quantitative blood culture and for determination of differential time to positivity and a sample from a peripheral vein for both quantitative and conventional blood culture. Immediately after sampling, the central venous catheter was withdrawn, and the tip was sent to the microbiology laboratory for conventional culture.

We compared the yield of the 3 types of culture in predicting CR-BSI. Catheters connected to a subcutaneous reservoir, Swan-Ganz catheters, and all arterial catheters were excluded from the study. No antibiotic-coated catheters were used in our intensive care unit during the study period.

Information obtained about these patients included age, sex, underlying disease, duration of hospitalization, duration of intensive care unit stay, type of catheter, number of catheter lumens, insertion site, and indwelling time. We also evaluated patients for concomitant infections, therapy with antimicrobial agents, and outcome.

Sample collection. Samples were collected systematically from all patients. The skin samples were obtained by lifting the dressing and rubbing the area around the insertion site (in a 3-cm radius) with a dry cotton swab. The inner hub samples were obtained using alginate swabs that were introduced into the hub and rubbed repeatedly against its inner surface (1 swab per hub). Blood for quantitative culture was obtained from a peripheral vein and through all different catheter hubs. Each sample contained ~10 mL of blood and was inoculated in Isolator tubes (Isolator 10; Wampole) for quantitative culturing by the lysis-centrifugation method, as described elsewhere [14–16]. We also simultaneously drew 10 mL of blood from each hub and from a peripheral vein to ascertain differential time to positivity using conventional blood cultures. All blood culture bottles were immediately taken to the microbiology laboratory and placed in an automatic culture detector (Bactec 9240, Bactec Plus Aerobic/F; Becton Dickinson), which re-

corded culture positivity every 15 min according to changes in fluorescence related to microbial growth. The catheter-tip sample was taken after scrubbing the skin surrounding the insertion site with 2% chlorhexidine and cutting off the tip (distal 5-cm segment) using sterile scissors.

Laboratory procedures. All swabs were semiquantitatively processed immediately by streaking the entire surface of Columbia agar plates supplemented with 5% sheep's blood. Catheter tips were processed using the semiquantitative culture method of Maki and colleagues, as described elsewhere [17, 18].

The plates were incubated aerobically for 72 h at 35°C, and the number of colonies recovered was counted. Blood cultures were processed according to routine methods. The microorganisms recovered were fully identified by standard microbiological methods [19].

Definitions. Superficial cultures (cultures of skin and catheter hubs) were considered to be positive when the same microorganism (≥ 15 colony-forming units per plate) was isolated from peripheral blood following criteria reported elsewhere [8]. Quantitative blood cultures were defined as positive when the number of colony-forming units of bacteria or yeasts isolated per milliliter of catheter-drawn blood was at least 5 times greater than that of blood obtained from a peripheral vein [1]. Differential time to positivity was defined as the difference in time needed for blood samples drawn simultaneously through the central venous catheter hub and from a peripheral vein to yield positive culture results. As in previous studies, differential time to positivity was considered to be positive if the blood drawn through any of the central venous catheter hubs yielded positive results at least 120 min earlier than the positivity of a blood sample drawn simultaneously from a peripheral vein [1, 10]. Significant colonization of the catheter tip was defined as a positive semiquantitative catheter culture by the roll-plate method, whereby ≥ 15 colony-forming units were cultured from the catheter tip [17].

We defined CR-BSI as the presence of bacteremia or fungemia in a patient with clinical manifestations of infection and no other apparent source of bloodstream infection (with the exception of the catheter). A catheter-tip culture positive for the same microorganism by the roll-plate technique was also required [1]. Accordingly, the reference standard for the evaluation of the 3 conservative procedures to diagnose suspected CR-BSI was a positive result of quantitative and/or conventional culture of blood from a peripheral vein and a semiquantitative catheter-tip culture positive for the same microorganism.

Data analysis. CR-BSI and non-CR-BSI groups were compared using a 2-tailed Fisher's exact test for proportions (qualitative variables) or a 2-tailed Student's *t* test for means (quantitative variables). We obtained the sensitivity, specificity,

positive predictive value, negative predictive value, and accuracy of the different diagnostic techniques, compared with the reference technique. All values were calculated with a 95% CI following an exact binomial distribution. To compare sensitivities, specificities, and accuracies, we used the 2-tailed McNemar test for paired samples. Predictive values were evaluated by 2-tailed Fisher's exact test [20]. A logistic regression model was performed to independently evaluate the validity of the 3 methods. For the comparisons, $P < .05$ was considered to be statistically significant. Data were analyzed using the SPSS software package, version 11.5 (SPSS).

RESULTS

During the study period, a total of 237 episodes of suspected CR-BSI involving 138 patients occurred in the study population. Of these, 33 episodes (13.9%) were excluded from the study, because the sample set was not complete. Therefore, 204 episodes involving 125 patients were included in the study. After analysis, 28 of the episodes were confirmed as CR-BSI (13.7%). Of the remaining 176 episodes that were not confirmed as CR-BSI, 27 (13.2%) were bloodstream infections that were not catheter-related, 36 (17.6%) involved catheter-tip colonization only (with no microorganisms isolated from the peripheral blood samples), and the remainder were cases with negative peripheral blood culture results and noncolonized catheters.

When clinical variables and other features of the CR-BSI and non-CR-BSI groups were compared, we were unable to find any significant differences in the populations (table 1). Of the

28 cases of CR-BSI included in the analysis, 27 were monomicrobial infections, and 1 was a polymicrobial infection (table 2). Of the 29 significant microorganisms, 16 (55.2%) were gram-positive bacteria, whereas the others were gram-negative bacteria (7; 24.1%) or yeasts (6; 20.7%). The 27 episodes of bloodstream infection with no catheter origin (including 4 polymicrobial infections) had the following etiological agents: 21 (63.6%) were gram-positive bacteria, 8 (24.2%) were gram-negative bacteria, and 4 (12.1%) were yeasts.

Table 3 shows a comparison of the validity values from the 3 conservative techniques for the diagnosis of CR-BSI. Differential time to positivity proved to be the most sensitive technique (sensitivity, 96.4%; 95% CI, 81.7%–99.9%) and the technique with the greatest negative predictive value (negative predictive value, 99.4%; 95% CI, 96.6%–99.9%). These differences were statistically significant when compared with differential quantitative blood cultures (sensitivity, 71.4%; negative predictive value, 95.6%). However, the technique that was most specific and had the highest positive predictive value was differential quantitative blood cultures (specificity, 97.7% [95% CI, 94.3%–99.4%]; positive predictive value, 83.3% [95% CI, 62.6%–95.3%]), especially when compared with differential time to positivity. Overall, the most accurate technique was differential quantitative blood cultures (accuracy, 94.1%; 95% CI, 90.0%–96.9%), followed by differential time to positivity (accuracy, 91.2%; 95% CI, 86.4%–94.7%) and semiquantitative superficial cultures (accuracy, 90.2%; 95% CI, 85.3%–93.9%), although there were no statistically significant differences be-

Table 1. Demographic and clinical data for patients with suspected catheter-related bloodstream infection (CR-BSI).

Variable	Patients with CR-BSI (n = 28)	Patients without CR-BSI (n = 176)	P	All patients (n = 204)
Age, mean years (95% CI)	65.9 (61.1–70.7)	66.8 (64.9–68.7)	.72	66.7 (64.9–68.4)
Male sex	17; 60.7 (40.6–78.5)	106; 60.2 (52.6–67.5)	.99	123; 60.3 (53.2–67.1)
Solid-organ tumor, mean no. of patients (95% CI) ^a	17.9 (6.1–36.9)	8.0 (4.4–13.0)	.15	9.3 (5.7–14.2)
Duration of catheter use, mean days (95% CI)	16.6 (12.4–20.9)	16.0 (14.5–17.5)	.77	16.1 (14.7–17.5)
Type of catheter				
Central venous, nontunneled tip	26; 92.9 (76.5–99.1)	172; 97.7 (94.3–99.4)		198; 97.1 (93.7–98.9)
Central venous, tunneled tip	0; 0 (0–12.3)	0; 0 (0–2.1)	.19	0; 0 (0–1.8)
Other	2; 7.1 (0.9–23.5)	4; 2.3 (0.6–5.7)		6; 2.9 (1.1–6.3)
Catheter insertion site				
Internal jugular vein	12; 42.9 (24.5–62.8)	80; 45.5 (37.9–53.1)		92; 45.1 (38.1–52.2)
Subclavian vein	16; 57.1 (37.2–75.5)	82; 46.6 (39.1–54.2)	.63	98; 48.0 (41.0–55.1)
Femoral vein	0; 0 (0–12.3)	9; 5.1 (2.4–9.5)		9; 4.4 (2.0–8.2)
Other	0; 0 (0–12.3)	5; 2.8 (0.9–6.5)		5; 2.5 (0.8–5.6)
Lumens, mean no. (95% CI)	2.9 (2.7–3.1)	2.9 (2.8–3.0)	.99	2.9 (2.8–3.0)
Receipt of parenteral nutrition	13; 46.4 (27.5–66.1)	67; 38.1 (30.9–45.7)	.41	80; 39.2 (32.5–46.3)
Polyurethane composition of catheter	28; 100 (87.7–100)	176; 100 (97.9–100)	.99	204; 100 (98.2–100)
Differential time to positivity >120 min	27; 96.4 (81.7–99.9)	17; 9.7 (5.7–15.0)	<.001	44; 21.6 (16.1–27.9)

NOTE. Data are no. of patients; percentage (95% CI), unless otherwise indicated.

^a None of the patients received chemotherapy in the 2 weeks before the study.

Table 2. Etiology of 28 cases of catheter-related bloodstream infection.

Microorganism	No. (%) of isolates (n = 29)
Coagulase-negative staphylococci ^a	11 (37.9)
Enterobacteriaceae ^b	7 (24.1)
Yeast ^c	6 (20.7)
<i>Staphylococcus aureus</i> ^d	3 (10.3)
<i>Enterococcus faecium</i> ^e	2 (6.9)

^a Includes 9 *Staphylococcus epidermidis* isolates (7 were methicillin-resistant strains) and 2 *Staphylococcus* species isolates (all were methicillin-resistant strains).

^b Includes 5 *Serratia marcescens* isolates, 1 *Enterobacter aerogenes* isolate, and 1 *Enterobacter cloacae* isolate. There were no multidrug-resistant strains.

^c Includes 3 *Candida parapsilosis* isolates, 2 *Candida albicans* isolates, and 1 *Saccharomyces cerevisiae* isolate (all yeasts were susceptible to amphotericin B, fluconazole, itraconazole, and voriconazole, except for the *S. cerevisiae* isolate, which was resistant to itraconazole).

^d All isolates were methicillin resistant.

^e Both isolates were ampicillin resistant.

tween values. When the logistic regression model was adjusted to evaluate the hypothesis of independence of the 3 methods, all 3 showed statistical significance with respect to the reference standard.

DISCUSSION

To our knowledge, this is the first prospective study comparing 3 techniques for the diagnosis of CR-BSI without catheter withdrawal involving patients without blood disorders or neutropenia who had central venous catheters and were hospitalized in the intensive care unit. No statistically significant differences in accuracy were detected among the techniques. Convenience, use of resources, and expertise should, therefore, determine the technique of choice in different medical settings.

CR-BSIs are the main cause of nosocomially acquired sepsis

in all populations, but they are particularly prevalent among patients admitted to the intensive care unit. Incidence density ranges from 3.9 to 30 episodes of CR-BSI per 1000 days of central venous catheter use, and mortality associated with CR-BSI is estimated to be 9%–43% [21–25].

It is common practice in many intensive care units to remove all central venous catheters from patients with sepsis, but on many occasions, watchful waiting is a prudent approach, and many cases can be empirically managed without immediate catheter withdrawal [26, 27]. In addition, >50% of catheter tips cultured in microbiology laboratories are found to be sterile [5, 6, 12, 14, 28, 29]. Furthermore, some CR-BSIs in hemodynamically stable patients can be handled in situ using antibiotic or antiseptic lock therapy. Frequently, bacteremia is cleared, and the catheter is sterilized [30].

The classic reference method to confirm CR-BSI consists of the concomitant isolation of the same microorganism from blood samples and the catheter tip [31]. Unfortunately, this requires catheter withdrawal and culture of the catheter tip, which, as we have mentioned, is frequently premature and unnecessary.

The most commonly reported techniques for assessing the catheter tip without catheter removal (i.e., conservative techniques) include the so-called superficial cultures, the differential colony counts between peripheral blood and blood obtained from the catheter hubs, and—more recently—differential time to positivity. To date, these 3 procedures have not been prospectively compared for adult patients hospitalized in the intensive care unit.

In 1990, we reported on a prospective study in which superficial cultures were semiquantitatively obtained immediately before catheter withdrawal. For 139 central venous catheter tips, superficial cultures had a positive predictive value of 66.2% and

Table 3. Comparison of the validity values (95% CI) of 3 techniques for the detection of catheter-related bloodstream infection.

Measure	Semiquantitative superficial cultures ^{a,b}	Differential quantitative blood cultures ^{a,c}	Differential time to positivity ^{b,c}
Sensitivity	78.6 (59.0–91.7)	71.4 (51.3–86.8)	96.4 (81.7–99.9)
Specificity	92.0 (87.0–95.6)	97.7 (94.3–99.4)	90.3 (85.0–94.3)
Positive predictive value	61.1 (43.5–76.9)	83.3 (62.6–95.3)	61.4 (45.5–75.6)
Negative predictive value	96.4 (92.4–98.7)	95.6 (91.4–98.1)	99.4 (96.6–99.9)
Accuracy	90.2 (85.3–93.9)	94.1 (90.0–96.9)	91.2 (86.4–94.7)

NOTE. $P < .05$ was considered to be statistically significant.

^a P values for the comparison of validity values between semiquantitative superficial cultures and differential quantitative blood cultures were: sensitivity, .75; specificity, .01; positive predictive value, .09; negative predictive value, .79; and accuracy, .15.

^b P values for the comparison of validity values between semiquantitative superficial cultures and differential time to positivity were: sensitivity, .13; specificity, .61; positive predictive value, .99; negative predictive value, .12; and accuracy, .83.

^c P values for the comparison of validity values between differential quantitative blood cultures and differential time to positivity were: sensitivity, .04; specificity, <.001; positive predictive value, .10; negative predictive value, .04; and accuracy, .29.

a negative predictive value of 96.7% in the diagnosis of catheter colonization. In patients with bloodstream infection, the hub is frequently the source of CR-BSI, and negative hub and skin culture results almost rule out catheter colonization and CR-BSI [8, 12, 32–35]. In the present study, sterile semiquantitative cultures of the hubs and skin had a negative predictive value of 96.4% for the catheter origin of a bloodstream episode.

The differential in quantitative bacteremia between blood samples obtained through the catheter hubs and peripheral blood samples is currently accepted as a confirmatory criterion for CR-BSI [14, 16, 36–42]. However, the technique is tedious, requires handling of blood samples by laboratory personnel, involves frequent contamination, and is expensive [43].

In 1998, Blot et al. [10]—and, several months later, Rogers and Oppenheim [44]—reported that the information provided by automated continuous monitoring blood culture systems could help in the diagnosis of catheter-related sepsis. Time to positivity and length of lag period were strongly related to the concentration of bacteria inoculated.

In 1999, Blot et al. [45] reported that a cutoff differential time to positivity of ≥ 120 min had 91% specificity and 94% sensitivity for the diagnosis of CR-BSI in a prospective study performed in the intensive care unit of a cancer center. The number of patients involved in the study was very limited (98 episodes were studied, and 17 patients were found to have CR-BSI), and most cases occurred in patients with long-term catheters.

Rijnders et al. [46] performed a study in a medical-surgical intensive care unit involving 100 consecutive adult patients whose catheters were to be removed because of suspected CR-BSI. Only 3 patients had CR-BSI, and 9 patients did not have CR-BSI. Rijnders et al. [46] did not find differences in median differential time to positivity between patients with CR-BSI and patients without CR-BSI, and they rejected the differential time to positivity as being of no use for the diagnosis of CR-BSI.

Studies comparing the yield of differential time to positivity with more conventional techniques have mainly been performed in cohorts of patients with blood disorders who have long-term catheters [13, 47]. Raad et al. [13] described 191 bloodstream infections with positive simultaneous central venous catheter tip and peripheral blood culture results. One hundred and eight patients had CR-BSI, and 83 did not have CR-BSI. A differential time to positivity of ≥ 120 min was associated with 81% sensitivity and 92% specificity for patients with short-term catheters and 93% sensitivity and 75% specificity for patients with long-term catheters, but the accuracy of the test was considerably reduced for patients receiving antimicrobial agents.

In a meta-analysis that evaluated the diagnosis of vascular CR-BSI, Safdar et al. [48] concluded that paired quantitative blood cultures were the most accurate test for the diagnosis of

CR-BSI. However, most other methods that were studied showed acceptable sensitivity and specificity ($>75\%$ for both) and negative predictive value ($>99\%$). The positive predictive value of all tests increased greatly with high pretest clinical probability.

In our series, the higher sensitivity and negative predictive value of differential time to positivity, compared with quantitative blood cultures (96.4% and 99.4% vs. 71.4% and 95.6%, respectively), were statistically significant when analyzed individually ($P = .04$). However, differential quantitative blood cultures with a quotient of >5 represented the best specificity in the diagnosis of CR-BSI (97.7%).

Our results suggest that the negative predictive value for each of the 3 tests that we compared is very high and that they each allow us to rule out catheter colonization and CR-BSI. Differential time to positivity is less specific than differential quantitative blood cultures and, in our opinion, has the risk of promoting indiscriminate use of catheter hubs to obtain blood samples for culture, with the consequent risk of reporting false-positive results for bacteremia and CR-BSI. The need to alert the microbiology department and to incubate blood cultures immediately at reception is another drawback of this technique. The ease of performance, low cost, and wide availability of the techniques lead us to recommend combining semiquantitative superficial cultures and peripheral blood cultures to screen for CR-BSI, leaving differential quantitative blood cultures as a confirmatory and more specific technique.

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