

Difference in time to positivity is useful for the diagnosis of catheter-related bloodstream infection in hematopoietic stem cell transplant recipients

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Summary:

Catheter-related bloodstream infections are associated with recognized morbidity and mortality. Accurate diagnosis of such infections results in proper management of patients and in reducing unnecessary removal of catheters. We carried out a prospective study in a bone marrow transplant unit to assess the validity of a test based on the earlier positivity of central venous blood cultures in comparison with peripheral blood cultures for predicting catheter-related bacteremia. Between May 2002 and June 2004, 38 bloodstream infections with positive simultaneous central venous catheter and peripheral vein blood cultures were included. A total of 22 patients had catheter-related bacteremias and 16 had noncatheter-related bacteremias, using the catheter-tip culture/clinical criteria as the criterion standard to define catheter-related bacteremia. Differential time to positivity of 120 min or more was associated with 86% sensitivity and 87% specificity. In conclusion, differential time to positivity of 120 min or more is sensitive and specific for catheter-related bacteremia in hematopoietic stem cell transplant recipients who have nontunnelled short-term catheters.

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diagnostic methods have been proposed to differentiate CRIs from non-CRIs.⁴ Although the quantitative catheter-tip culture technique is sensitive and specific, it is of no value in salvaging a CVC.^{5,6} To avoid unnecessary removal of the CVC, simultaneous quantitative blood cultures from the catheter and the peripheral vein have been developed. This method has been limited because of the expense and the labor-intensive process involved.^{7,8} Recently, Blot *et al*^{9,10} reported that measurement of differential time to positivity (DTP) between the peripheral and CVC blood cultures is highly sensitive and specific for the diagnosis of catheter-related bloodstream infection (CRBI) in patients with long-term catheters. DTP was defined as the difference in the time it took for a blood culture drawn through the CVC and a culture drawn from a peripheral vein to become positive. Since then, four studies have confirmed the utility of DTP for the diagnosis of CRI in patients with cancer,^{11–14} and one study of adults in a medical surgical ICU did not confirm its utility.¹⁵

Four of these studies^{9–11,15} used the catheter-tip-culture/clinical criteria as the criterion standard, two studies used paired quantitative blood cultures,^{12,13} and one study¹⁴ used both methods.

The aim of the present prospective study was to assess the validity of DTP for the diagnosis of CRBI in hematopoietic stem cell transplant (HSCT) recipients with nontunnelled short-term (<30 days) CVCs using the catheter-tip culture/clinical criteria as the criterion standard to define CRI.

Materials and methods

Patient population

Between May 2002 and June 2004, we prospectively monitored all patients admitted to the 'National Centre for Bone Marrow Transplantation' (Tunis) with febrile neutropenia and a nontunnelled CVC in place. The study protocol was approved by the local medical ethical committee, and written informed consent was obtained from the patients or their legal representatives.

To be eligible for the study, patients had to have had a HSCT, a nontunnelled short-term (<30 days) CVC; a fever of >38°C; a neutrophil count <0.5 × 10⁹/l; a complete set of blood cultures (see below) obtained at the time of

In patients with central venous catheters (CVCs), catheter-related infections (CRIs) are a prominent cause of morbidity, excess hospital costs, and in some cases, mortality.^{1–3} However, despite their high frequency of occurrence and seriousness, such infections are often difficult to diagnose. During the past 3 decades, numerous

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inclusion in the study, and a pathogen isolated from at least one blood culture.

Exclusion criteria were presence of a CVC on admission; catheterization for more than 30 days; contraindication to the use of subclavian catheterization due to a major blood coagulation disorder (platelet count $<50 \times 10^9/l$, disseminated intravascular coagulation); an absence of catheter-tip culture at the time of catheter removal.

Data collection

Standardized data collection forms were completed for all patients. These data included demographic characteristics, underlying disease, therapy (allogeneic or autologous stem cell transplantation), catheter insertion and removal date. Additional data recorded were the presence of local signs and symptoms of infection at the catheter insertion site (swelling, warmth, tenderness, or purulent discharge), duration of fever, presence or absence of antimicrobial therapy at the time of inclusion, type and dosage of antimicrobial regimen during the entire episode, clinical response to antimicrobial therapy and/or catheter removal, neutrophil count on day of insertion, and duration of neutropenia.

Catheter insertion

CVCs were external nontunnelled short-term, polyurethane double lumen catheters (Arrows, Readings, USA). Catheter sizes were chosen appropriate to age (5 or 7 French diameter). The physician wore mask, cap, sterile gloves, and surgical gowns and used large sterile drapes. The skin insertion site was disinfected with povidone iodine. All CVCs were placed in the subclavian vein by the infra-clavicular approach, by the same experienced physician, in the operating room. Catheters were inserted percutaneously, using the Seldinger technique.¹⁶ The CVC tip was confirmed radiographically to lie in the superior vena cava. Study catheters were not exchanged over guidewires.

Insertion sites were covered with a transparent sterile dressing (Tegaderm, Health Care, USA). Catheter care included changing the dressing under aseptic conditions every 6 days.

Microbiologic methods

After rigorous antiseptic cleansing of the skin and the hub with povidone iodine, at least two sets of blood cultures were obtained simultaneously from the catheter hub of the CVC and from a peripheral vein (maximum of 15 min apart). For each blood culture set, a 20-ml blood sample was drawn aseptically (from the distal lumen, used for blood sampling and parenteral nutrition only) and inoculated into aerobic and anaerobic bottles (Vital-Duo, bioMérieux, France), immediately taken to the microbiology laboratory, and placed in the automatic positive-culture detector (Vital, bioMérieux), which records culture positivity every 15 min according to changes in fluorescence related to microbial growth. The shortest time to positivity of the first bottle in a set was noted. The difference between time to positivity of the peripheral (aerobic or anaerobic)

blood culture and the CVC blood culture was calculated and expressed in minutes. The DTP was considered indicative of CRBI at a cutoff limit of 2 h. Cases of positivity of the hub blood culture only, resulting in an 'infinite' DTP, were excluded in the analysis.

The identity of isolates from peripheral and CVC-positive blood cultures was assessed on the basis of colonial morphology, species identification, and identical antibiogram. Catheters were removed aseptically, at the discretion of primary care physicians, if they were no longer needed or if infection was suspected. A 5-cm segment of the removed catheter tip was aseptically cut and delivered to the microbiology laboratory for quantitative culture according to Brun-Buisson *et al*.¹⁷

Definitions and diagnosis

The criteria for CRBI were derived from those described by Raad and Bodey¹⁸ and were based on clinical symptoms and/or quantitative tip culture, taking into account the presence of bacteremia or fungemia, in all patients.

Definite CRBI was diagnosed when no detectable focus of infection except the catheter could be identified and one of the following criteria was present: (i) local purulence, increased warmth, and induration extending at least 2 cm from the insertion site or (ii) a positive quantitative catheter tip culture ($>10^3$ colony forming unit (cfu) per catheter) according to Brun-Buisson *et al*,¹⁷ with isolation of the same microorganism from the catheter and the bloodstream.

Likely CRBI was diagnosed when no apparent source of sepsis could be identified except for the catheter or when a distal source of infection could be identified with a microorganism different from the one in the bloodstream and one of the following criteria was present: (i) bacteremia or fungemia with a common skin organism (coagulase-negative staphylococcus, *Staphylococcus aureus*, or *Candida* sp.) in a patient with clinical manifestations of sepsis (fever, chills, or hypotension) or (ii) fever, chills, or hypotension occurring at the time of catheter connection.

Patients were classified as having CRBI when they had definite or likely CRBI.

Patients were classified as having bacteremia due to another source when no clinical signs of infection due to the catheter were present, when another focus of infection could be identified, and when the same microorganism was isolated from another source of infection and the bloodstream.

Patients were classified as having bacteremia from an unknown source when the source of the bacteremia could not be identified.

The principal investigator determined whether infections were catheter-related, and had no knowledge of DTP at the time of adjudication of the reference standard definition.

Analysis and statistics

We divided the study sample into two groups: those with catheter-related bloodstream infection and those without. We determined the significance of the differences between the two study groups using the χ^2 test or the Fisher exact

test, as appropriate, for categorical variables. The Student's *t*-test or Mann-Whitney test was used for continuous variables. All *P*-values were based on two-tailed tests (level of significance, *P*<0.05). Sensitivity, specificity, and likelihood ratios, along with associated 95% confidence intervals (CIs), were determined for DTP of 120 min or more.

Results

From May 2002 to June 2004, a total of 420 pairs of simultaneously drawn blood cultures were analyzed. Of these, 315 pairs (75%) had negative CVC blood cultures and peripheral vein blood cultures, 42 pairs (10%) had positive CVC blood cultures and negative peripheral vein blood cultures, and 21 pairs (5%) had negative CVC blood cultures and positive peripheral vein blood cultures. We excluded these 378 pairs of cultures from the analysis because the study's objective was to evaluate DTP when both cultures were positive. Another 42 pairs of cultures (10%) had positive results on both the CVC blood cultures and peripheral vein blood cultures. Of these, we excluded four pairs because the CVC blood cultures and peripheral vein blood cultures grew different organisms. We included in the analysis the remaining 38 pairs, which were positive simultaneous blood cultures that grew the same organism. The main characteristics of the 38 patients are shown in Table 1. CVCs were removed and cultured in all patients included in this study. We found 22 CRBIs and 16 non-CRBIs, according to the definitions described earlier. Patients with CRBI were more likely to have a shorter duration of neutropenia (8 vs 14 days, *P*=0.04) and a

higher frequency of staphylococcal bacteremia (68 vs 37.5%, *P*=0.02).

At the onset of bacteremia, CVCs were in place for a median of 9 days (8–27 days) and only 30% of the 38 patients were receiving antibiotics when simultaneous blood cultures were drawn. Catheters were removed after a median of 2 days (0–14 days) following the onset of bacteremia. Only 35% of the 38 patients were receiving antibiotics at the time of catheter removal.

DTP of 120 min or more was associated with high sensitivity and specificity, as shown in Table 2.

Discussion

Data from our study show that a DTP of 120 min or more is sensitive and specific in diagnosing CRBI associated with the use of short-term catheters, in HSCT recipients. In our study, we used the catheter-tip culture/clinical criteria as the criterion standard to define CRBI.

Our results support the findings of Raad *et al*¹⁴ who recently reported in a large study (*n*=191) the diagnostic utility of DTP for short-term (<30 days) and long-term (>30 days) catheters. In this study, they relied on a composite definition of CRBI proposed by the Infectious Disease Society of America (IDSA),¹⁹ which, in the absence of any other probable source of bacteremia, includes simultaneous quantitative blood cultures or semiquantitative catheter-tip culture.

However, when they used semiquantitative catheter-tip cultures alone to establish the definition of CRBI, the specificity of DTP was only 45%, and there were 36 false-positive results (DTP>120 min and a negative catheter

Table 1 Characteristics of patients with positive simultaneous blood cultures that grew the same organism

	Patients with CRBI (n = 22)	Patients with non-CRBI (n = 16)	P-value
Male, n (%)	12 (54)	9 (56)	0.12
Female, n (%)	10 (46)	7 (44)	0.13
Median age, years (range)	24 (5–59)	26 (7–60)	0.26
<i>Underlying disease, n (%)</i>			
Leukemia	10 (45)	7 (44)	0.31
Lymphoma	7 (32)	4 (25)	0.22
Myeloma	5 (23)	5 (31)	0.19
Median duration of hospitalization, days (range)	32 (12–35)	33 (13–37)	0.35
Median duration of catheter, days (range)	28 (9–29)	27 (9–28)	0.42
Autologous SCT ^a , n (%)	16 (73)	11 (69)	0.37
Allogeneic SCT ^a , n (%)	6 (27)	5 (31)	0.46
Median duration of neutropenia ^b , days	8 (5–15)	14 (7–22)	0.04
<i>Blood culture organisms, n (%)</i>			
Coagulase-negative staphylococci	15 (68)	6 (37.5)	0.02
<i>Pseudomonas aeruginosa</i>	2 (9)	2 (12.5)	0.34
<i>Enterobacter cloacae</i>	1 (4.6)	0	0.27
<i>Klebsiella oxytoca</i>	1 (4.6)	2 (12.5)	0.16
<i>Escherichia coli</i>	1 (4.6)	1 (6.2)	0.48
<i>Corynebacterium</i> spp.	1 (4.6)	2 (12.5)	0.15
<i>Proteus mirabilis</i>	0	1 (6.2)	0.19
<i>Candida albicans</i>	1 (4.6)	2 (12.5)	0.16

^aSCT: stem cell transplantation.

^bDefined as an absolute neutrophil count <0.5 × 10⁹/l.

Table 2 Diagnostic utility of differential time to positivity (DTP)

DTP ^a results (min)	CRBF ^a (n)		Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
	Yes	No				
≥120	19	2	86 (80–92)	87 (79–93)	6.6 (3.8–12.1)	0.16 (0.08–0.2)
<120	3	14				

^aDTP = differential time to positivity; CRBI = catheter-related bloodstream infection.

Table 3 Studies that evaluated the differential time to positivity method

Reference	Definition	Design	Evaluable patients (n)	Sensitivity (%)	Specificity (%)
Blot <i>et al</i> ⁹	Tip culture	Retrospective	42	96	100
Blot <i>et al</i> ¹⁰	Tip culture	Prospective	28	94	91
Seifert <i>et al</i> ¹²	Quantitative blood culture (> 5:1 ratio)	Prospective	51	82	86
Rijnders <i>et al</i> ¹⁵	Tip culture	Prospective	10	66	43
Gaur <i>et al</i> ¹³	Quantitative blood culture (> 5:1 ratio)	Prospective	33	88	100
Raad <i>et al</i> ¹⁴	Tip culture plus quantitative blood culture	Prospective	191	89	83
Current study	Tip culture	Prospective	38	86	87

culture). In 34 of these 36 patients, the CVC was removed more than 24 h after obtaining the blood cultures, and in that interval patients received antibiotics through the catheter for at least 24 h. Therefore, most of the 'false-positive' results could have been true-positive results in which the catheter culture serving as the gold standard became falsely negative because of antibiotic exposure.

In our study, despite the use of catheter culture as gold standard, the specificity of DTP was 87%, and there were two false-positive results (DTP > 120 min and a negative catheter culture). This difference may be attributed to removal of the CVC before antibiotic exposure. Only 35% of the 38 patients were receiving antibiotics at the time of catheter removal.

Rijnders *et al*¹⁵ published a study evaluating the DTP in the diagnosis of catheter-related bloodstream infections in critically ill patients and concluded that this method is associated with a low specificity and predictive value in patients with short-term catheters. The low specificity and predictive values in that study may be attributed to the small number of patients with positive simultaneous blood cultures ($n = 10$) and to the large number of patients (78%) who were receiving antibiotics when the simultaneous blood cultures were drawn (in our study, only 30% of the patients were receiving antibiotics when simultaneous blood cultures were drawn).

Main studies^{9,10,12–15} that have evaluated the DTP method are shown in Table 3.

Our study has several limitations. First, samples were obtained from the distal lumen only (samples obtained from both lumens should be cultured, and the culture with shortest time to detection should be used for calculating the DTP). Second, all patients included in this study had received a HSCT. To evaluate generalizability, further studies are needed to investigate the utility of this diagnostic test in a broader, heterogeneous patient population.

In conclusion, our results confirm the usefulness of the DTP technique for *in situ* diagnosis of CRBI in HSCT

recipients with short-term CVCs. This diagnostic method, which avoids unnecessary catheter removal, could be coupled with early targeted antimicrobial intervention such as antibiotic lock therapy^{20,21} and could result in improved patient care in this highly compromised patient population.

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