Bloodstream Infection in Neutropenic Cancer Patients Related to Short-Term Nontunnelled Catheters Determined by Quantitative Blood Cultures, Differential Time to Positivity, and Molecular Epidemiological Typing with Pulsed-Field Gel Electrophoresis

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To determine the rate of catheter-related bloodstream infection (CRBSI) among cases of primary bloodstream infection (BSI) in febrile neutropenic cancer patients with short-term nontunnelled catheters, quantitative paired blood cultures (Isolator) from the central venous catheter (CVC) and peripheral vein were obtained between November 1999 and January 2001. Bactec blood culture bottles were obtained to determine the differential time to positivity (DTP). CRBSI was defined as a quantitative blood culture ratio of >5:1 (CVC versus peripheral) with proven identity of isolates from positive peripheral and CVC blood cultures as confirmed by pulsed-field gel electrophoresis. Forty-nine episodes of primary BSI were detected among 235 cancer patients with febrile neutropenia. Of these, 18 episodes (37%) were CRBSI and 31 (63%) were BSI with an unknown portal of entry. Coagulase-negative staphylococci were present in nine cases of CRBSI (50%). The identity of isolates from peripheral and CVC blood cultures was confirmed in all cases. Earlier positivity (>2 h) of CVC-drawn versus peripheral blood cultures was observed in 18 of 22 CRBSI-associated blood cultures (sensitivity, 82%; specificity, 88%; positive predictive value, 75%; negative predictive value, 92%). In summary, CRBSI accounted for 37% of cases of primary BSI in this population of neutropenic cancer patients. DTP compares favourably with quantitative blood cultures for the diagnosis of CRBSI and may be particularly useful for patients in whom catheter salvage is highly desirable.

The diagnosis of catheter-related bloodstream infection (CRBSI) in cancer patients with febrile neutropenia remains difficult. Typical clinical signs such as tenderness or purulent discharge at the insertion site, implicating the catheter as the source of infection, are frequently absent during neutropenia. The absence of any other likely source of the bloodstream infection (BSI) does not permit one to distinguish between the two major portals of entry for BSI in these patients, i.e., the catheter and the gastrointestinal tract. Clinicians usually avoid removal of the catheter in patients with febrile neutropenia that would permit a semiquantitative or quantitative catheter tip culture because reinsertion of a new central venous catheter (CVC) carries a substantial bleeding risk. Consequently, existing data on the epidemiology of CRBSI in cancer patients is restricted mainly to nonneutropenic patients with long-term tunnelled or nontunnelled catheters or totally implanted ports that had been removed for diagnostic and/or therapeutic purposes (7; I. I. Raad, H. A. Hanna, S. McFadyen, K. Marts, D. Richardson, R. Y. Hachem, and P. Mansfield, Program Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. K2049, 2001). However, little is known about the frequency of CRBSI among cases of primary BSI in febrile cancer patients

with short-term catheters who are profoundly neutropenic and in whom the catheter usually remains in place.

Currently, quantitative blood culture (QBC) techniques involving paired blood cultures obtained from the central catheter hub and from a peripheral vein are regarded as the “gold standard” for the diagnosis of CRBSI if catheter removal is undesirable or impossible (22). Blot et al. have described a new method that compares the differential time to positivity (DTP) as determined by a continuous blood culture-monitoring system for qualitative blood cultures drawn simultaneously from the catheter and from a peripheral vein (1, 2). Compared with the diagnostic criteria proposed by Raad and Bodey (18) and the results of quantitative catheter tip culture, the authors found the DTP a reliable tool for the diagnosis of CRBSI in cancer patients with long-term catheters.

The aim of the present study was to assess whether measurement of the DTP could offer accuracy comparable to that of differential QBC for the diagnosis of CRBSI in neutropenic patients with short-term CVCs, i.e., nontunnelled catheters that are usually removed before discharge from hospital, that remain in place. In addition, the rate of CRBSI among cases of primary BSI in patients with hematologic malignancies and febrile neutropenia was determined.

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MATERIALS AND METHODS

Facility description. The Cologne University Hospital is a 1,380-bed, tertiary-care teaching hospital which houses a 68-bed adult hematology-oncology unit. Annually, about 1,200 patients are admitted for the diagnosis and treatment of hematologic malignancies and 450 episodes of chemotherapy-induced neutropenia are observed. Trimethoprim-sulfamethoxazole or ciprofloxacin given orally is the routine prophylactic antimicrobial regimen in these patients. Empirical therapy instituted for febrile neutropenia is usually either ceftriaxone plus gentamicin or piperacillin-tazobactam or meropenem. All microbiologic support for the hospital is managed at the Institute of Medical Microbiology, Immunology and Hygiene.

Study design. Between November 1999 and January 2001, we prospectively monitored all patients admitted to the hematology department of Cologne University Hospital with febrile neutropenia and an indwelling, nontunnelled CVC in place. To be eligible for the study, patients had to have a hematologic malignancy as the primary disease, such as acute myelogenous leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, or multiple myeloma; a nontunnelled short-term CVC, a fever of $\geq 38.0^{\circ}\text{C}$, a neutrophil count of $\leq 500/\mu\text{l}$, a complete set of blood cultures (see below) obtained at the time of inclusion in the study, and a pathogen isolated from at least one blood culture. Follow-up blood cultures representing the same bacteremic episode were included and analyzed separately. Second episodes were included provided that more than 7 days had elapsed since resolution of signs and symptoms of the previous BSI and that an organism different from the pathogen from the first episode was isolated. For the purpose of this study, these episodes were considered different cases.

Patient data. For each patient the following data were recorded: the underlying malignancy, the type of catheter, the site of catheter insertion, the duration for which the catheter had been in place before the first positive blood culture was obtained, the presence of local signs and symptoms of infection at the catheter insertion site (e.g., swelling, warmth, tenderness, or purulent discharge), the duration of fever, the presence or absence of antimicrobial therapy at the time of inclusion, the type and dosage of the antimicrobial regimen during the entire episode, the clinical response to antimicrobial therapy and/or catheter removal, the duration of neutropenia, and outcome.

Microbiological methods. At least two sets of blood cultures were obtained simultaneously from the catheter hub of the CVC and from a peripheral site. For each blood culture set, a 20-ml blood sample was drawn aseptically and inoculated into aerobic and anaerobic Bactec (Bactec Plus Aerobic/F and Bactec Plus Anaerobic/F; Becton Dickinson, Heidelberg, Germany) blood culture bottles (6 ml each) and into an Isolator tube (8 ml; Oxoid, Wesel, Germany). For multi-lumen catheters, blood was drawn from the distal port (used for blood sampling and parenteral nutrition only). Blood cultures were transported to the microbiology laboratory and processed within 6 h. Before being processed, the blood cultures were held at room temperature. Conventional blood culture bottles were incubated in an automatic blood culture detection system (Bactec 9240) that allowed continuous monitoring of blood cultures for microbial growth, and the shortest time to positivity of the first bottle to become positive in a set was noted. The difference between the time to positivity of the peripheral—aerobic or anaerobic—blood culture and the CVC blood culture (the DTP) was calculated and expressed in minutes. Isolator tubes were cultured by the lysis centrifugation technique. Blood culture bottles and agar plates derived from Isolator tubes were incubated at $36 \pm 1^{\circ}\text{C}$ for 7 days. The DTP was considered indicative of CRBSI at a cutoff limit of 2 h. Cases of positivity of the hub blood culture only, resulting in an infinite DTP, were included in the analysis provided that the absolute time to positivity did not exceed 12 h, indicating a high primary inoculum and making contamination less likely. The isolation of common skin organisms such as coagulase-negative staphylococci (CoNS), micrococci, or viridans streptococci from a single blood culture set with a time to positivity of >12 h, indicating a low inoculum, was considered to represent contamination. These cases were excluded from further evaluation.

Catheters were removed at the clinician's discretion and cultured by the semiquantitative roll-plate method (13).

Bacterial isolates from positive blood cultures were identified to species level using conventional methods; CoNS were identified by the ID 32 Staph system (Biomérieux, Marcy-L'Etoile, France) as specified by the manufacturer. The antimicrobial susceptibilities of the strains were determined by the disk diffusion technique as recommended by NCCLS (16). Methicillin resistance of staphylococci was confirmed by the E test (AB Biodisk, Solna, Sweden). Isolates were stored at -70°C on porous beads (Microbank; Mast Diagnostics, Reinfeld, Germany) until further use. The identity of isolates from peripheral and CVC positive blood cultures was assessed on the basis of colonial morphology, species

identification, and identical antibiogram and confirmed by pulsed-field gel electrophoresis (PFGE) of bacterial genomic DNA (4).

Diagnosis of catheter-related bloodstream infection. The paired QBC method was used as the gold standard (3). CRBSI was defined by (i) the presence of clinical features of BSI, (ii) a QBC ratio of $>5:1$ (CVC versus peripheral) with proven identity of isolates from peripheral and CVC positive blood cultures as confirmed by PFGE, and (iii) the absence of any other likely source of infection. Isolation of >100 CFU/ml from the CVC QBC was also considered indicative of CRBSI if no organisms were cultured from the peripheral blood culture (3).

For comparison only and not for establishing the diagnosis of CRBSI, the criteria proposed by Raad and Bodey were used (18). These criteria are based on a primary BSI with no other apparent source for the infection in which clinical and/or microbiological evidence implicates the catheter as the source of infection. The clinical and microbiological evidence could be one of the following: (i) a positive semiquantitative catheter tip culture (≥ 15 CFU) and isolation of the same microorganism from the catheter and from a blood culture; (ii) an exit-site infection (manifested by erythema, warmth, induration, or local purulence) due to the same organism as that isolated from the bloodstream; or (iii) resolution of the clinical sepsis within 48 h of catheter removal while the patient is receiving no active antimicrobials or after an unsuccessful trial of active antibiotics for at least 72 h.

RESULTS

Study population. From 24 November 1999 to 11 January 2001, 235 blood culture sets were received from 115 cancer patients with 181 episodes of febrile neutropenia and with a nontunnelled CVC in place. Among these, 73 Bactec blood cultures were positive, accounting for a positivity rate of 31%. Fifty-nine blood cultures obtained from 43 patients with 49 episodes of febrile neutropenia represented true bacteremia, and 14 were considered to represent contamination (contamination rate, 6%). Six patients experienced a second bloodstream infection. The patients had a mean age of 48 years (range, 19 to 79 years); 24 patients (56%) were male. Underlying malignancies in these patients included acute myelogenous leukemia ($n = 21$), non-Hodgkin's lymphoma ($n = 10$), Hodgkin's disease ($n = 3$), acute lymphoblastic leukemia ($n = 3$), and multiple myeloma ($n = 2$).

At the onset of bacteremia, CVCs were in place for a mean of 12 days (median, 10 days; range, 1 to 38 days). All catheters were triple-lumen noncoated catheters; 26 of them had been placed into the subclavian vein, and 23 had been placed into the internal jugular vein.

Evaluation of blood cultures. A single set of paired blood cultures was obtained in 42 bacteremic episodes, 4 patients had two sets taken, and 3 patients had three sets taken. Forty-nine episodes of primary BSI were detected in these patients. Episodes of secondary BSI were not observed.

Among cases of true bacteremia, 51 blood culture sets had both positive Bactec blood culture bottles and Isolator tubes. Only these cases were primarily considered for comparison of QBC and DTP for the diagnosis of CRBSI. Eight cases had only positive Bactec blood cultures while the Isolator tubes showed no growth. The calculated sensitivity of the lysis centrifugation technique for detection of bacteremia was 86%. Four Isolator tubes (1.7%) were thought to be contaminated. In two cases, no growth was detected in the corresponding Bactec blood cultures; in another two cases, true bacteremia was detected by Bactec blood cultures but a different organism was isolated in small numbers (1 to 2 CFU) from the corresponding Isolator tube. In fact, no true-positive Isolator-positives, Bactec-negative blood cultures were observed.

Eighteen episodes (37%) were CRBSI as determined by the

TABLE 1. Blood cultures associated with CRBSI as determined by QBC and absolute time to positivity and DTP of paired Bactec blood cultures

Microorganism	CVC-to-peripheral colony count ratio	Absolute time to positivity (h)	DTP (h)
<i>E. coli</i> ^{a,b}	1,000,000	4.0	Infinite
<i>S. maltophilia</i> ^{a,b}	1,000,000	10.0	Infinite
<i>S. maltophilia</i> ^a	1,000,000	18.0	15.0
<i>E. faecalis</i> , <i>Bacillus</i> spp.	76,900	5.5	4.0
CoNS	28,500	9.0	4.0
CoNS	13,333	9.0	4.0
<i>Lactobacillus</i> spp.	6,666	2.0	15.7
<i>K. oxytoca</i>	5,000	1.0	6.0
CoNS	200	9.9	5.5
CoNS ^{a,b}	200	8.0	Infinite
CoNS ^a	150	7.0	7.0
CoNS ^{a,b}	150	8.0	Infinite
CoNS ^a	100	12.0	5.0
CoNS ^a	100	12.0	10.0
<i>P. aeruginosa</i>	100	12.0	5.0
CoNS	63	7.0	10.0
<i>S. aureus</i>	60	11.5	-1.3
CoNS	50	10.0	6.0
CoNS	10	13.0	0.0
<i>P. aeruginosa</i>	10	14.0	0.0
CoNS	8	14.0	3.0
<i>S. oralis</i> , <i>S. salivarius</i>	6	6.0	1.0

^a CVC QBC positive with heavy to confluent growth (10^2 to 10^6 CFU/ml) but peripheral QBC remaining negative.

^b Only Bactec hub culture positive with heavy to confluent growth (10^2 to 10^6 CFU/ml) on agar plate derived from positive hub QBC.

paired QBC method. BSI with an unknown portal of entry was detected in 31 episodes (63%). Twenty-two QBCs obtained from 18 patients showed a CVC-to-peripheral colony count ratio of $>5:1$ and were thus considered to indicate CRBSI (Table 1). Included were eight cultures with heavy (>100 CFU) or confluent growth observed in the CVC QBC while the peripheral QBC showed no growth. In 18 of these 22 blood cultures, the DTP of the paired peripheral and hub Bactec blood cultures was >2 h, accounting for a sensitivity of 81.8% for the diagnosis of CRBSI. In four of the eight cases with positive quantitative hub cultures only, both peripheral and hub-drawn Bactec blood cultures were positive, with a DTP of >2 h. In the remaining four cases, only the hub-drawn Bactec blood culture was positive (with time to positivity ranging from 4 to 10 h), leading to an infinite DTP with heavy (>150 CFU) to confluent growth on the agar plate derived from the CVC-drawn QBC. The DTP was >2 h in another four cases (false positives) that were not considered CRBSI by the differential QBC method (specificity, 86.2%, positive predictive value [PPV], 81.8%; negative predictive value [NPV], 86.2%) (Fig. 1).

In a second step, the evaluation was extended to all 73 positive blood cultures including those with positive Bactec

FIG. 1. QBC ratio (CVC versus peripheral) and DTP of blood cultures from neutropenic patients with and without CRBSI.

blood cultures only and those representing contamination. Among these, another two false-positives were observed. The resulting specificity of the DTP for the diagnosis of CRBSI was 88.2%, with a PPV of 75.0% and an NPV of 91.8%.

Blood culture results sometimes differed during a single episode of BSI. In a patient with Hodgkin's disease, low colony counts in the CVC and peripheral QBC obtained on day 1 of febrile neutropenia were indicative of low-grade bacteremia with CoNS, probably resulting from mucosal lesions in the gastrointestinal tract. The following day, blood culture colony counts fulfilled the criteria of CRBSI, probably resulting from hematogenous seeding, but colony counts were still low. Another 2 days later, heavy growth was observed in the CVC blood culture, giving evidence of confirmed CRBSI. The dynamic evolution of CRBSI in this patient is illustrated in Table 2.

Microbiology. The distribution of pathogens recovered from the bloodstream of neutropenic cancer patients is shown in Table 3. The most common pathogens isolated both from cases of CRBSI and from cases of BSI with an unknown portal of entry were CoNS, accounting for 41 and 37% of isolates, respectively. While *Escherichia coli*, *Klebsiella* spp., and viridans group streptococci were recovered in descending order of frequency in cases of BSI with an unknown source, no other pathogen was predominantly involved in CRBSI.

In 39 of the 49 cases (80%), the same pathogens were isolated both from the blood culture taken from the CVC and from the blood culture taken simultaneously from a peripheral site. Corresponding isolates ($n = 46$) were compared by PFGE. The PFGE patterns of all these isolates were identical, including 21 strains of CoNS (Fig. 2).

Antimicrobial therapy. At the time of inclusion in the study, 21 patients were receiving antimicrobial therapy: 9 patients

TABLE 2. Evolution over time of a CRBSI in a patient with CoNS bacteremia

Day	CVC/peripheral colony count	CVC/peripheral colony count ratio	Absolute time to positivity (h)	DTP (h)
0	12/7 CFU	1.7	12.0	1.0
1	8/1 CFU	8.0	14.0	3.0
3	Confluent growth/35 CFU	28,500	9.0	4.0

TABLE 3. Organisms isolated from blood cultures of 43 neutropenic cancer patients with 49 primary BSI

Microorganism	No. (%) of organisms isolated from:		
	All episodes (n = 49)	CRBSI (n = 18)	Unknown source (n = 31)
CoNS	24 (38.1)	9 (40.9)	15 (36.6)
<i>E. coli</i>	10 (15.9)	1 (4.5)	9 (22.0)
<i>Klebsiella</i> spp.	5 (7.9)	1 (4.5)	4 (9.8)
Viridans group streptococci	5 (7.9)	2 (9.1)	3 (7.3)
<i>Enterobacter</i> spp.	3 (4.8)	1 (4.5)	2 (4.9)
<i>S. maltophilia</i>	3 (4.8)	2 (9.1)	1 (2.4)
<i>Candida</i> spp.	3 (4.8)	1 (4.5)	2 (4.9)
<i>S. aureus</i>	2 (3.2)	1 (4.5)	1 (2.4)
<i>E. faecalis</i>	2 (3.2)	1 (4.5)	1 (2.4)
<i>P. aeruginosa</i>	1 (1.6)	1 (4.5)	0
<i>Proteus</i> spp.	1 (1.6)	0	1 (2.4)
<i>S. agalactiae</i>	1 (1.6)	0	1 (2.4)
<i>Corynebacterium</i> spp.	1 (1.6)	0	1 (2.4)
<i>Bacillus</i> spp.	1 (1.6)	1 (4.5)	0
<i>Lactobacillus</i> spp.	1 (1.6)	1 (4.5)	0
Polymicrobial bacteremia	10 (20.4)	2 (11.1)	8 (25.8)

were receiving trimethoprim-sulfamethoxazole and 4 were receiving ciprofloxacin orally as prophylactic regimen, while 8 patients were receiving intravenous antimicrobial therapy. No data were available for the remaining nine patients. In only three patients, isolates recovered from blood cultures were found to be susceptible to the antimicrobial administered before BSI.

Clinical presentation and outcome. Signs and symptoms of local inflammation were present in 12 cases (4 [22%] of 18 patients with CRBSI as determined by the QBC method and 8 [26%] of 31 patients without CRBSI). Eleven of these patients showed only a minor inflammation; purulent discharge requiring a bacteriological culture was not observed. Resolution of signs and symptoms of BSI within 48 h after catheter removal without antibiotic treatment was observed in only 5 cases (2 [11%] of 18 patients with CRBSI as determined by the QBC

method and 3 [10%] of 31 patients without CRBSI); however, in most patients, empirical antimicrobial therapy that was effective against the offending pathogen had been instituted before catheter removal.

Catheters were removed after a mean of 9 days (median, 6 days; range, 0 to 40 days) following the onset of BSI. In 8 patients (16%), the CVC was removed within 24 h, and another 21 catheters were removed between days 2 and 10 after onset of BSI. However, in only four cases was catheter removal performed before the institution of antimicrobial therapy. Significant growth obtained by the roll-plate culture method of an organism identical to the primary bloodstream pathogen was seen in 10 cases; in another 8 cases, <15 CFU of an organism identical to the primary bloodstream pathogen were recovered. Overall, the diagnostic criteria proposed by Raad and Bodey (18) would have correctly identified only four cases of CRBSI. In two other patients with CRBSI, the semiquantitative tip culture was positive not until day 10 after onset of BSI. In another seven patients, CRBSI would have been diagnosed based on conventional diagnostic criteria that was not confirmed by the QBC method.

Six patients died during hospitalisation, accounting for an in-hospital mortality rate of 12%. Death occurred 2, 6, 17, 34, 36, and 62 days after onset of the BSI. Thus, only two cases of BSI were considered possibly related to death, with *Stenotrophomonas maltophilia* and *Candida albicans* being the offending pathogens.

DISCUSSION

Clinical criteria alone are unreliable for establishing the diagnosis of intravascular device-related infection. This is especially true for neutropenic cancer patients, in whom fever of unknown origin is frequent, clinical findings implicating the catheter as the cause of infection are often absent, and early empirical antimicrobial therapy is usually instituted without or long before removal of the catheter. The diagnosis of CRBSI in patients with febrile neutropenia has therefore been difficult or impossible unless QBCs were performed.

Diagnostic methods for CRBSI that do not require catheter removal include surveillance skin and hub cultures, the endoluminal brush method, and the Gram stain and acridine-orange leukocyte cytospin test (6, 10, 11). Blot et al. have developed the concept that measurement of the DTP of cultures of blood drawn from the catheter hub and from a peripheral site permits the diagnosis of CRBSI without removal of the catheter and offers an attractive and cost-effective alternative method to QBC (2). This method has been evaluated prospectively in cancer patients mainly with solid-organ tumors in the intensive care unit setting whose catheters were removed for suspected CRBSI (1, 14). The reported sensitivities in these two studies were 94 and 81% with specificities of 91 and 100%, respectively. The majority of patients with confirmed CRBSI had long-term catheters that had been in place for up to 4 years (1). Conversely, when evaluating the DTP for the diagnosis of CRBSI in intensive care unit patients with short-term intravascular catheters, Rijnders and colleagues observed a high rate of false-positive results and concluded that DTP is not useful for the diagnosis of CRBSI in the intensive care unit (19). In another prospective study, Raad et al. did not see major dif-

FIG. 2. Fingerprint patterns of CoNS genomic DNA obtained by PFGE after restriction with *Sma*I. Lanes: 1 and 20: molecular size marker; 2 to 17, corresponding *S. epidermidis* blood isolates obtained from the catheter hub and from peripheral sites in seven patients; 18 and 19, *S. haemolyticus* blood isolates.

ferences when evaluating DTP (>2 h) for the diagnosis of CRBSI associated with short-term and long-term CVCs (I. I. Raad, H. A. Hanna, B. Alakech, I. Chatzinikolaou, K. V. I. Rolston, E. Whimbey, and J. Tarrand, Prog. Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. K1426, 2000). The reported sensitivity was 94%, with a specificity of 91 and 89%, respectively. However, no data were given in this abstract publication on how long the short-time CVC had been in place. Differences in the duration for which catheters had been in place might have accounted for the difference in results.

In the present study, we prospectively evaluated the usefulness of the DTP technique for diagnosing CRBSI in neutropenic patients with hematologic malignancies. Only patients with short-term, nontunnelled catheters were included. We used paired QBCs and a CVC-to-peripheral culture colony count ratio of >5:1 as the gold standard for diagnosing CRBSI (3, 5, 17, 22).

With the differential QBC technique, we detected 18 episodes of CRBSI among the 49 episodes of primary BSI in cancer patients with febrile neutropenia (37%) including 8 episodes with positive hub cultures only. For the remaining 31 episodes of BSI (63%), the gastrointestinal tract is the most probable portal of entry.

Our results confirm that the DTP of blood cultures drawn simultaneously from the hub and from a peripheral site is a simple method for the diagnosis of CRBSI without catheter removal even in patients with short-term catheters. Of the 22 blood culture sets from patients with CRBSI, 18 had a DTP of >2 h. The DTP at this cutoff limit had 82% sensitivity, 86% specificity, 82% PPV, and 86% NPV for the diagnosis of CRBSI. These results did not change when the cutoff level was extended to 3 h.

To reflect clinical practice when a comparative method is not available and the diagnosis of CRBSI has to be based on DTP findings only, we extended our evaluation to include all positive blood cultures including those that were considered related to BSI originating from the gastrointestinal tract and those that were considered to represent contamination. Taking these results together, the sensitivity (82%) and specificity (88%) of the DTP technique (>2 h) did not change. However, while the PPV was lower (75%), the NPV rose to 92%.

In our study, the diagnostic criteria proposed by Raad and Bodey (18) were not very useful. CVCs remained in place for at least 48 h following the onset of BSI in 84% of neutropenic patients and, for the vast majority of patients, were not available for culture before institution of empirical antimicrobial therapy. Similarly, resolution of fever could only rarely be correlated with catheter removal. Semiquantitative culture results of catheter tips were often not in agreement with those obtained by the QBC method. One explanation for this discrepancy could be that catheter tips were not removed until blood culture result had become available, i.e., several days after the onset of BSI. By this time, a primary BSI originating from a mucosal lesion might have resulted in significant catheter colonization by hematogenous seeding, as we were able to demonstrate in one patient. On the other hand, antimicrobial therapy administered before catheter removal could have led to false-negative catheter tip cultures.

The situation when only the CVC blood culture is positive

remains an issue of controversy. Blot et al. excluded these cases in their first retrospective study (2). In their prospective study, Blot et al. confirmed CRBSI in only 3 of 17 cases where only the hub culture was positive but did not consider these cases when analyzing the sensitivity and specificity of the DTP method (1). To reliably detect these cases by the DTP technique, cases with infinite DTP have to be included. In the present study, we found eight patients with CRBSI as determined by the QBC technique in whom only the quantitative hub culture was positive. In four of these cases, only the hub-drawn Bactec blood culture was positive, leading to an infinite DTP. We were able to differentiate between true CRBSI as determined by QBC and contamination by including hub-only positive blood cultures with an infinite DTP only if the absolute time to positivity did not exceed 12 h and heavy to confluent growth was observed on the agar plate derived from the CVC QBC, thus arguing strongly against contamination. One might argue that this cutoff limit is too conservative because in cases of CRBSI caused by CoNS the absolute time to positivity ranged from 7 to 14 h. However, it is our primary goal to avoid unnecessary catheter removal in cases of CoNS bacteremia of uncertain significance despite a possible overlap in absolute time to positivity between cases of true bacteremia and contamination (23). We suggest not using or extending this cutoff limit when *Candida* spp., *Pseudomonas aeruginosa*, *S. maltophilia*, or other organisms are recovered that usually require prolonged incubation periods before blood cultures become positive.

Not surprisingly, CoNS were recovered most frequently from cases of CRBSI. Of interest, CoNS were also found with similar frequency in cases of primary BSI where the gastrointestinal tract is the most likely portal of entry. This suggests that CoNS might initially enter the bloodstream from a mucosal lesion and result in CRBSI by hematogenous seeding. We were able to prove this concept in a patient with Hodgkin's disease by observing that three sequential blood cultures taken over a period of 3 days yielded CoNS, with only the second and third blood cultures giving evidence of confirmed CRBSI.

PFGE analysis has been used by several researchers to assess strain relatedness and to determine the significance of CoNS isolated from multiple blood cultures (9, 21). Two recent studies have shown that fewer than half of the patients with two or more blood cultures positive for CoNS had the same strain (8, 20). To our knowledge, our study is the first to use molecular typing of strains isolated from differential blood cultures obtained for the diagnosis of CRBSI. PFGE analysis of all available isolate pairs recovered from hub and peripheral blood cultures yielded identical fingerprint patterns.

The DPT technique and the QBC method have one significant limitation that was not specifically addressed in previous studies. Both paired QBCs and Bactec blood cultures have to be processed without major delay to maintain the inoculum ratio between the CVC and peripheral blood culture present at the time when the blood cultures were drawn. In a preliminary in vitro study, this difference was maintained if the blood cultures were kept at room temperature for up to 8 h (data not shown). A longer preincubation time may lead to false-negative DTP results. This implies that laboratory personnel should be available 24 h a day for processing and incubation of blood cultures bottles.

In conclusion, our results confirm the usefulness of the DTP technique for the in situ diagnosis of CRBSI in neutropenic cancer patients 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 (12, 15) and could result in improved patient care in this highly compromised patient population. Although our data do not suggest that prior antimicrobial therapy may lead to misclassification of primary BSI, larger prospective studies are necessary to assess the influence of prior administration of broad-spectrum antibiotics on the diagnostic yield and accuracy of the DTP technique.

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