Utility of daily catheter-drawn blood cultures to predict catheter-related bacteremia in hematopoietic stem cell transplanted patients

Kateterden günlük alınan kan kültürlerinin hematopoietik kök hücre nakli yapılan hastalarda kateter ile ilişkili bakteriyemiyi öngörmedeki yararı

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Abstract

Objective: There is no diagnostic tool to identify which bacterial catheter colonization may eventually result in bloodstream infection. We speculated that a faster growth or repeated positivity of serial blood cultures drawn from the catheter might herald catheter-related bacteremia (CRB) before the onset of fever.
Material and Methods: We designed a prospective observational pilot study. All patients who underwent hematopoietic stem cell transplantation (HSCT) were prospectively included in the study over 10 months. Daily catheter-drawn blood cultures (DBC) were performed. We recorded the growth time of each blood culture and bacterial isolation. A fast-growing blood culture (positive <12 hours) or at least 2 positive identical cultures within 4 consecutive days in the DBC were defined as a marker of risk for CRB. The value of this marker to predict CRB was investigated.
Results: A total of 82 patients (843 days of catheter) were included in the study. Fast- growing or repeated identical cultures were present in 20 patients; among them, 15 had clinical criteria of CRB. Among 62 patients without fast-growing or repeated identical cultures, 11 met the criteria of CRB. Consequently, for the defined marker of risk, the positive predictive value was 75%, negative predictive value 82%, sensitivity 70%, and specificity 91%. Sixty-two blood cultures were needed to detect one case of CRB prior to the onset of fever.
Conclusıon: The use of routinely drawn catheter-blood cultures does not seem to be a useful tool for predicting CRB in HSCT patients. *(Turk J Hematol 2009; 26: 67-71)*
Key words: Catheter-related bacteremia, hematopoietic stem cell transplantation, diagnosis, infectious complication

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Özet

Amaç: Hangi bakteriyel kateter kolonizasyonunun sonuçta kan dolaşımı enfeksiyonuna yol açabileceğini belirleyecek tanısal bir araç mevcut değildir. Kateterden alınan seri kan kültürlerinde daha hızlı üremenin veya tekrarlı pozitifliğin, ateşin başlangıcından önce, kateter ile ilişkili bakteriyeminin (KİB) habercisi olabileceği tahmin edilmektedir.

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Yöntem ve Gereçler: Prospektif gözlemsel bir pilot çalışma tasarladık. Hematopoietik kök hücre nakli (HKHN) yapılan tüm hastalar 10 ayı aşkın bir süre boyunca prospektif olarak çalışmaya dahil edildi. Kateterden günlük kan kültürü alındı. Her kan kültürü için üreme zamanı ve bakteriyel izolasyon kaydedildi. Hızlı üreme görülen bir kan kültürü (pozitif <12 saat) veya ardışık 4 gün içinde en az 2 pozitif özdeş kültür, KİB riski için belirteç olarak tanımlandı. Bu belirtecin KİB öngörmedeki değeri araştırıldı.
Bulgular: Çalışmaya toplam 82 hasta (843 kateter günü) dahil edildi. Kültürde hızlı üreme veya tekrarlı özdeş kültürler 20 hastada mevcuttu, bu hastalardan 15'i KİB klinik kriterlerine sahipti. Kültürlerinde hızlı üreme görülmeyen veya tekrarlı özdeş kültürlere sahip olmayan 62 hasta arasında 11'i KİB klinik kriterlerine sahipti. Bu nedenle, tanımlanan risk belirteci için, pozitif prediktif değer %75, negatif prediktif değer %82, sensitivite %70 ve spesifite %91 idi. Ateşin başlangıcından önce kateter ile ilişkili bir bakteriyemi olgusunu belirlemek için 62 kan kültürü gerekli idi.
Sonuç: Hematopoietik kök hücre nakli yapılan hastalarda kateter ilişkili bakteriyemiyi öngörmek için kateterden rutin alınan kan kültürlerinin kullanımı, yararlı bir araç gibi görünmemektedir. *(Turk J Hematol 2009; 26: 67-71)*
Anahtar kelimeler: Kateter ile ilişkili bakteriyemi, hematopoietik kök hücre nakli, tanı, infeksiyöz komplikasyon

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Introduction

Infectious complications constitute an important cause of morbidity and mortality in patients who undergo hematopoietic progenitor transplantation (HSCT). Bloodstream infections are among the most frequent bacterial infections in these patients, and central vascular catheters are a very common source of the bacteremia [1,2]. Catheter-related bacteremia (CRB) is an increasing-in-frequency and potentially life-threatening complication.

Some studies have shown that differential time to positivity of peripheral and catheter-drawn blood cultures seems to be highly predictive of CRB at the onset of fever [3,4]. However, there is no diagnostic tool to identify the bacterial colonization eventually predictive of ulterior bloodstream infection [5,6]. A method to diagnose the colonization of a vascular catheter before the onset of bacteremia would be potentially useful in an attempt to prevent CRB episodes.

It is supposed that the catheter surface undergoes a bacterial colonization with a biofilm formation [7]. There may be a critical level of biofilm development above which substantial cell detachment and embolism occur, with bloodstream infection and fever occurrence [8]. The number of organisms released from the biofilm to the blood may be related to the time to the blood culture growth in the automatic device detector system.

We speculated that faster growth of serial blood cultures drawn from the catheter might be a potentially useful way to anticipate the diagnosis of CRB.

Materials and Methods

This study was performed in the hematopoietic progenitor transplantation unit-ward in the Hospital Clinic, Barcelona (Spain) over 10 months. We designed an observational and prospective pilot study. The study was approved by the Ethical Committee.

Adult patients with a double lumen vascular catheter insertion in the jugular vein prior to the conditioning regimen for hematopoietic progenitor transplantation were prospectively included in the study. All the catheters were non-tunneled. All patients had line placement just before HSCT, and no one had catheter for previous treatments. Prophylaxis with vancomycin was routinely performed at the time of catheter insertion. Patients did not receive any other anti-bacterial prophylaxis.

As per protocol, an aliquot of routinely catheter-drawn blood sample for blood count (distal lumen) was obtained daily. The first 5 ml of blood, essentially containing blood for the catheter, were immediately cultured in aerobic media. We did not use this distal lumen in the previous 4-6 hours (h). We chose a 5 ml aliquot instead of standard 10 ml because this blood had maximum probabilities to contain bacteria and to avoid extra blood extractions. Blood cultures were processed by means of an automatic infrared device system (Bactec 9240, Beckton Dickinson Diagnostic Instrument Systems; Sparks, Maryland, USA) for 5 days. This automatic culture detector detects and records culture positivity periodically, according to changes in CO_2 concentration related to microbial growth.

Daily blood extraction for culture (DBC) was performed since patients were admitted to the unit until the onset of fever or the use of antibiotics for any other reason. Clinicians were unaware of the results of the DBC unless the patients developed fever. At the onset of fever, additional aerobic and anaerobic blood cultures (10 ml of blood each) were obtained from both distal and proximal lumen of the catheter. Then, broad-spectrum antibiotics were administered through the catheter.

The time to growth of blood cultures was recorded for each isolation, and expressed in hours. We also recorded for each patient the bacterial isolation and the time to positivity in each case, the data regarding the infusion of blood progenitors, and the data regarding the onset of fever.

The catheter was not routinely removed unless considered clinically necessary; therefore, we could not use the Centers for Disease Control (CDC) definitions to diagnose CRB. Blood cultures were drawn from the central venous catheter.

The criteria to diagnose CRB were positive catheter tip culture (roll-plate technique) and bacterial isolation in blood cultures or the existence of the same bacterial isolation in two blood cultures at the onset of fever without evidence of other clinical source of infection or fever.

We defined a marker of risk of CRB as the presence of: 1) a fast-growing blood culture (positive in <2 h) in any of the daily blood cultures, or 2) at least 2 positive identical cultures within 4 consecutive days in the DBC. We chose a cut-off of 12 h to

predict CRB because a time to positivity higher than 12 h may reflect a colony forming unit count (CFU/ml) of 103 for coagulase-negative staphylococci; this cut-off is used in many diagnostic methods for detection of CRB [9].

The value of this marker of risk to predict CRB by the same microorganism was investigated. Statistical analysis was performed with the SPSS software, ver. 13. We calculated negative and positive predictive value and sensitivity and specificity of the marker of risk. Changes in the mean time to positivity were analyzed by Wilcoxon test.

Results

A total of 82 patients were included in the study. During the period of the study, 843 days of catheter were recorded, and a total of 927 blood cultures were performed. Positive blood cultures were determined in 131 cases. All patients developed fever in 10.3±3.6 days (mean±SD) after the catheter placement. The infusion of progenitor was performed 7.2±3 days (mean±SD) after the catheter placement.

In 36 patients (44%), no bacteria were isolated in the daily or fever-related blood cultures.

Twenty-eight cases had bacterial blood isolation at the time of fever (Table 1). In two cases, there were other additionally obvious causes of fever (*Pneumocystis jirovecii* pneumonia and drug-induced fever). Among the remaining 26 cases, there were 15 cases with the same bacterial isolation at DBC and at the onset of fever, and therefore only 15 met our criteria for diagnosing CRB (17.8 cases of infection per 1000 days of catheter). According to our definition of CRB and in our series, the catheter infection was the responsible factor in 57.7% (15/26) of the febrile episodes in HSCT patients with bacterial isolations at the onset of fever. Of these 15 patients, coagulase-negative staphylococci were isolated in 10 patients, *Escherichia coli* in two patients, and *Pseudomonas aeruginosa, Aerobacter* spp, and *Staphylococcus aureus* in the other three patients. A culture of the tip of the catheter was performed in six of these 15 patients, and was positive in the six cases (Table 1).

Of the 26 patients with a positive isolation at the time of fever, five presented different microorganisms in the DBC and fever-related culture, and six patients had negative DBC. One patient with negative DBC presented a positive culture for the catheter tip (Table 1).

In 18 patients, there was a bacterial isolation in some blood extraction during the study (Table 1). These discordant results were found in the following situations:

1) Five patients presented positive DBC but negative fever-related blood culture. All isolations corresponded to coagulase negative *staphylococci.*

2) Thirteen patients presented just one positive blood culture of the DBC with negative fever-related blood culture. Coagulase-negative *staphylococci* was isolated in 10 cases, S. mitis in one case, *Micrococcus spp* in one case, and *Lactobacillus* spp in one case. The time to positivity was longer than 15 h in all cases. One patient presented a positive catheter tip culture.

Table 1. Type and number of isolation

	No.	Bacteria	Positive catheter tip
Positive FBC and DBC	20		
Concordant DBC/FBC	15	Coagulase-negative *staphylococci* (n=10)	6
		E. coli (n=2)	
		S. aureus (n=1)	
		P. aeruginosa (n=1)	
		Aerobacter spp (n=1)	
Discordant DBC/FBC	5		
Positive FBC and negative DBC	8	Coagulase-negative *staphylococci* (n=5)	1
		Gram-negative bacilli (n=2)	
		S. epidermidis (n=1)	
Positive >1 DBC and negative FBC	5	Coagulase-negative *staphylococci* (n=5)	
Positive 1 DBC and negative FBC	13	Coagulase-negative *staphylococci* (n=10)	1
		S. mitis (n=1)	
		Micrococcus spp (n=1)	
		Lactobacillus spp (n=1)	
Negative FBC and DBC	36		

DBC: Daily drawn blood cultures; FBC: Fever-related blood cultures; Positive >1 DBC: More than one positive blood culture during DBC; Positive 1 DBC: Only one positive blood culture during DBC; No: Number of cases; Concordant DBC/FBC: Same bacteria isolated in daily drawn and fever-related blood cultures; Discordant DBC/FBC: Different bacteria isolated in daily drawn and fever-related blood cultures

Mean time to positivity decreased from 25.1±5 h on the second day of the study to 10.7±5.8 h on the 11th day of the study (p=0.043, Wilcoxon test).

A marker of risk of CRB was present in 20 patients, of whom 15 had clinical criteria of CRB. Of the 62 patients without the marker of risk, 11 met the criteria of CRB. These data meant that for the defined marker of risk of CRB, the positive predictive value was 75% (15/20), negative predictive value 82% (51/62), sensitivity 70% (15/26) and specificity 91% (51/56). The number of blood cultures needed to detect one case of CRB prior to the onset of fever was 62.

Discussion

The search for a method to diagnose CRB has elicited an important controversy [10], and there is no useful diagnostic tool to predict CRB [11]. A very early diagnosis would allow a correct treatment before the onset of bacteremia and would avoid bacterial metastatic seeding and complications.

To date, there are no clinically useful tools for identifying patients who are more likely to develop CRB [5,6]. The usefulness of serial blood cultures in predicting CRB in standard clinical practice is not high. Biofilm formation with a progressive increase in the catheter colonization might increase the likelihood of developing clinically relevant CRB [12]. Our data showing a shorter time to growth for positive blood cultures in conjunction with an increase in time from catheter insertion is in agreement with the biofilm theory. Nevertheless, we found that the time to positivity applied to serial catheter-drawn blood cultures does not seem to add clinically relevant information. In fact, with our criteria, 62 blood cultures were needed to predict a single case of CRB. There might be several reasons underlying these results. First, bacteria might be intermittently shed from the biofilm to the blood, and the moment of blood extraction may be different from the moment of bacterial release [8]. A once-daily extraction might miss many of these bacterial sheds. Second, most patients develop fever from a variety of sources a few days after HSCT. At this time, regardless of the origin of the fever, serial catheter-drawn cultures were stopped and most patients received wide spectrum endovenous antibiotics that most likely would affect catheter colonization. This further reduces the potential usefulness of serial catheter-drawn blood cultures in HSCT, but does not exclude its potential use in other clinical settings.

Our study has some relevant limitations. First, catheters were not routinely removed in all cases after the appearance of fever; therefore, the diagnosis was not based on standard recommendations, such as CDC definitions. Although the gold standard for the diagnosis of CRB relies on these criteria, it is not very common to remove the catheter in actual practice in HSCT patients, unless there is high suspicion of CRB (e.g. identical isolation from vein and catheter-drawn blood cultures). In fact, attending clinicians were not aware of the routine DBC, in order to prevent a biased clinical attitude. In addition, we tried to avoid further inconvenience to the patients. Many patients had important complications related with venous punctures, including thrombocytopenia. The responsible clinicians did not always find adequate peripheral blood extraction (besides catheter drawing) for febrile patients in the absence of data of severe sepsis. Our study thus tried to provide some meaningful information while avoiding further inconvenience to the patient or interference with the criteria of the attending clinician.

The Centers for Disease Control (CDC) definitions include the isolation of bacterium from blood culture obtained from a peripheral vein in a patient with an intravascular catheter and a positive catheter culture with the same microorganism [13]. However, the peripheral vein is sometimes a difficult access and several authors have explored others definitions with clinical criteria [14], modified surveillance case definitions [15] or periodic cultures, like us [16].

A single blood culture might be positive for several reasons, e.g. contamination, bloodstream infection, or colonization of the catheter, but repeated blood cultures with the same bacterial isolation diminishes the probability of contamination. In the case of colonization of the catheter, bacteria isolated in the blood cultures reflect bacterial colonies within the catheter, which eventually may pass to the blood and shed to other places. This is precisely one of the points of interest of our paper: catheter colonization may herald bloodstream infection. Unfortunately, our hypothesis that routine non-aggressive evaluation might be potentially useful for an early identification of patients with a high risk of catheter-derived bloodstream infections was not supported by our data.

Another potential criticism of our work is the lack of genetic studies from concordant bacterial isolates to confirm the common origin of infection. However, some authors and preliminary results from our laboratory have reported that different bacterial populations (particularly coagulase-negative staphylococci) might be present in the catheter biofilm [17]. Therefore, a discordant genetic pattern of bacterial isolates would not necessarily exclude a single source of bacteria, namely the catheter biofilm. In any event, if genetically discordant cases were discarded as cases of CRB, this would not increase the yield of our diagnostic protocol.

The operational growth time of 12 h selected in this study could be debated. Time to growth depends not only on the density of the microorganisms (crucial parameter for interpretation) and the quantity of blood, i.e. the bacterial inoculum, but also heavily on the type of microorganism. The use of different time definitions for early growth for different bacterial isolations would have complicated the design of our study and it is questionable whether this would provide a more useful approach. How to determine the most appropriate time for every microorganism is also unclear. (We did an exploratory analysis with shorter and longer periods of time (data not shown) and did not find any improvement in the ability to predict bacteremia). On the other hand, we tried to maximize the standardization of variables at the time of the design of the study, such as the quantity of blood. In any event, our results do not support the use of fast growth in routinely drawn blood cultures as a predictor of CRB.

In summary, our results are compatible with the theory of biofilm formation as a mechanism involved in the pathogenesis of CRB. However, the use of routine catheter- drawn blood cultures does not seem to be a useful tool for predicting CRB in HSCT patients.

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