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REVIEW ARTICLE

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New tools in diagnosing catheter-related infections

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Abstract Clinical criteria alone are insufficient to allow a diagnosis of intravascular catheter-related sepsis (CRS). A definite diagnosis of CRS usually requires removal of the catheter for quantitative catheter tip culture. However, only about 15–25% of central venous catheters (CVC) removed because infection is suspected actually prove to be infected, and the diagnosis is always retrospective. Other diagnostic tests, such as differential quantitative blood cultures from samples taken simultaneously from the catheter and a peripheral vein, have been proposed to avoid unjustified removal of the catheter and the potential risks associated with the placement of a new catheter at a new site: a central-to-peripheral blood culture colony count ratio of 5:1 to 10:1 is considered indicative of CRS. Despite its high specificity, the latter diagnostic technique is not routinely used in clinical practice because of its complexity and cost. The measurement of the differential time to positivity between hub blood (taken from the catheter port) and peripheral blood cultures might be a reliable tool facilitating the diagnosis of CRS in situ. In an in vitro study, we found a strong relationship between the inoculum size of various microorganisms and the time to positivity of cultures. When the times to positivity of cultures of blood taken simultaneously from central and peripheral veins in patients with and without CRS were examined, we found that earlier positivity of central vs peripheral vein blood cultures was highly correlated with CRS. Using a cut-off value of +120 min, the "differential time to positivity" of the paired blood samples, defined as time to positivity of the peripheral blood minus that of the hub blood culture, had 91% specificity and 94% sensitivity for the diagnosis of CRS. This method may be coupled with other techniques that have high negative predictive value, such as skin cultures at the catheter exit site. This diagnostic test can be proposed for routine clinical practice in most hospitals using automatic devices for blood cultures positivity detection. Endoluminal brushing of the catheter is considered sensitive and specific for the diagnosis of CRS, but the risk of embolisation or subsequent bacteraemia should be considered. Gram staining and the acridine-orange leucocyte cytospin test on through-catheter blood culture have been proposed for rapid diagnosis of CRS without catheter removal. The technique, which requires 100 μl catheter blood and the use of light and ultraviolet microscopy, is considered simple, rapid (30 min) and inexpensive. In conclusion. diagnostic tools such as paired blood cultures or Gram staining and the acridine-orange leucocyte cytospin test should allow a diagnosis of CRS without catheter removal in cancer patients.

Key words Catheter-related sepsis · Bacteraemia · Blood cultures · Differential time to positivity · Cancer patients

Introduction

Clinical criteria alone, such as fever or inflammation at the catheter entry site, are not sufficient to establish the diagnosis of infections related to a central venous catheter (CVC) [1–3]. A few years ago, Raad and Bodey proposed diagnostic criteria for catheter-related bacteraemia that were based on the clinical presentation and the results of blood cultures [4]. On the basis of these criteria, it may be assumed that *catheter-related sepsis (CRS)* is likely when no apparent source of sepsis is identified except the catheter, and that bacteraemia or fungaemia is due to a common skin organism (such as coagulase-negative staphylococci, propionibacterium, micrococcus, *bacillus* spp. etc.), *Staphylococcus aureus* or *Candida* spp. in a patient with clinical manifestations of sepsis (fever, chills or hypotension). In addition, a CRS may be considered likely in the case of a cure of the sepsis syndrome or return to a normal temperature within 48–72 h of catheter removal, or when fever, chills or hypotension occur at the time of catheter connection. *Definite CRS* is diagnosed when no detectable focus of infection except the catheter is identified and one of the following criteria is fulfilled: (a) presence of local purulence (with the same microorganism as in blood cultures), increased warmth and induration extending at least 2 cm from the CVC insertion site, (b) disappearance of signs of infection and a return to a normal temperature within 24 h after catheter removal without antibiotic treatment, (c) positive quantitative catheter culture, with isolation of the same microorganism from the catheter and bloodstream.

Traditionally, the *diagnosis* of CRS requires *removal of the catheter* or a *guidewire exchange* for culture of the catheter tip [5, 6]. In a recent meta-analysis, quantitative catheter cultures had the highest pooled sensitivity and specificity (above 90%) when compared with semiquantitative or qualitative (broth) cultures [7]. Because endoluminal contamination is the most frequent route of microbial seeding of prolonged indwelling vascular catheters, the quantitative methods, which take into account the external and internal surfaces of the device, appear to be especially appropriate for cancer patients with long-term catheters for chemotherapy. Ultrasonication or catheter vortexing are proposed for quantitative catheter tip culture [6, 8]. When a totally implanted port is removed because of suspected CRS, the catheter tip and the port itself should both be cultured.

However, the drawback of all quantitative catheter culture techniques is that the diagnosis is always retrospective, and only about 15–25% of CVC removed because of suspected infection are in fact found to be infected when a quantitative catheter culture is performed [3, 4]. Therefore, when catheter-related infection is suspected, it may be desirable to establish the diagnosis and to treat the infection without removing the catheter [9, 10] assuming the clinical situation is not life threatening and the catheter is still needed, especially in the case of coagulase-negative staphylococcal infection in immunocompromised patients.

Guidewire exchange of CVC in which CRS is suspected may be proposed. This technique is associated with fewer complications than new-site replacement, but seems to be linked to a greater risk of catheter-related infection [11, 12]. In addition, guidewire exchange may be difficult in cancer patients with long-term tunnelled catheters and is not available for totally implanted ports.

Diagnostic tests without catheter removal

To avoid unjustified removal of CVC and risks associated with placement of a new catheter in a new site, other tests have been proposed. Some techniques, such as in situ cultures (culture of the hub, or cultures of skin and exit site of the catheter), have a high sensitivity and negative predictive value; they are therefore destined to be used mainly to rule out the diagnosis of CRS [13–17]. Cultures of catheter entry site reflect mainly contamination by the extraluminal route, which predominates in the case of short-term catheters. Cultures of blood from the hub of the catheter reflect mainly contamination by the endoluminal mechanism, which predominates for long-term catheters, such as those used in cancer patients, and could be more useful than skin cultures in this subset of patients. However, both these techniques generally exhibit poor specificity [13–17]. In addition, skin and hub cultures may not be proposed for patients with totally implanted ports.

In order to confirm the diagnosis of CRS, techniques with high specificity and positive predictive value are needed. *Quantitative blood cultures* (QBC) are characterised by such properties. The principle of QBC is based on the following hypothesis: when a bacteraemia is linked to a catheter-related infection the number of microorganisms retrieved by the hub blood culture (taken from the catheter) is high, owing to a purging effect of the infected lumen of the catheter. The sensitivity of the method is increased when a simultaneous blood culture is taken from a peripheral vein: the comparison of the microbial count between hub and peripheral blood cultures shows an overload of bacteria on the central blood culture compared with the peripheral blood culture when a CRS is present. Conversely, when the bloodstream infection is not related to a catheter infection, the microbial counts of hub and peripheral blood cultures are similar.

In 1979, Wing et al. became the first to perform simultaneous hub and peripheral blood cultures in a patient suspected of having CRS, and they showed 10^4

and 25 colonies/ml, respectively, in the hub and peripheral blood cultures [18]. After removal of and culture from the catheter, the same microorganisms were found to be present at the catheter tip. Since this first study using quantitative blood cultures, several authors have attempted to assess the predictive value of QBC taken solely from the catheter with a threshold of positivity of 15 or 25 cfu/ml [1, 19]. Andremont et al. showed in cancer patients that the semiquantitative measurement of the number of microorganisms present in blood taken through the catheter (using a threshold of 10^3 cfu/ml) had a specificity of 99%, but a sensitivity of only 20% [9]. The decrease of the threshold to 10^2 or 10 cfu/ml reduced the specificity of the method significantly.

The concept developed by Wing et al. has been evaluated in several studies. When simultaneous quantitative blood cultures are performed, a significant differential colony count of 5–10:1 for the CVC vs the peripheral vein culture is indicative of CRS [20–22], although some discrepancy between differential quantitative blood cultures and semiquantitative catheter cultures has been reported [23]. The differential colony count does in fact most often exceed 50 or 100 in cases of proven CRS. Douard et al., using paediatric Isolator (DuPont) tubes, showed a specificity and a positive predictive value of 100%, while sensitivity and the negative predictive value were slightly lower (83% and 78%, respectively) [22]. This technique has been validated mainly for long-term catheters such as those used for parenteral nutrition or cancer therapy, and more recently for short-term catheters for ICU patients [24].

New diagnostic tools

Despite the high specificity of the method [20–22,, differential quantitative blood cultures are not routinely used in clinical practice, mainly because of their relative complexity and their cost. Therefore, the concept of *measurement* of the *differential time to positivity* between *hub blood and peripheral blood cultures* has been developed [25]. The automatic devices recently introduced in clinical microbiology practice measure the time to blood culture positivity. A given cut-off value, linked to the bacterial metabolism and to the number of microorganisms initially present in the bottle, indicates that bacterial or fungal multiplication has occurred in the bottle. The higher the initial bacterial inoculum, the more quickly this cut-off value is reached. Consequently, for central and peripheral blood cultures, comparing the times elapsing between bottle inoculation and the detection of positivity could constitute an alternative method to quantitative blood cultures.

In an in vitro study [25], investigated the relationship between the concentration of microorganisms and the time to positivity of culture. Several measurements were performed with clinical isolates of eight microorganisms: *S. aureus* and *S. epidermidis* (2 strains each), *E. faecalis, E. coli* and *P. aeruginosa* (3 strains each), *S. maltophilia, A. baumannii* and *C. albicans* (1 strain each). Ten-fold serial dilutions were then performed in saline water. Aerobic bottles were inoculated with 0.1 ml of each dilution and placed in an automatic positive culture detector, which detects and records positivity for each sample every 15 min based on changes in the level of fluorescence according to microbial growth. We found a linear relationship between the initial concentration of microorganisms and the time to positivity of culture for all species tested, although the growth rate varied from strain to strain. For example, a one $\log_{10}$ decrease in concentration of bacteria in the inoculum increased the time to detection of culture positivity by a mean of 142 min for *S. aureus*, by 148 min for *S. epidermidis*, 75 min for *Enterococcus faecalis*, 83 min for *Escherichia coli*, 97 min for *P. aeruginosa,* and 285 min for *Candida albicans* [25]. Similar results have been reported by other workers using continuous-monitoring blood culture systems for the diagnosis of CRS due to coagulase-negative staphylococci, with an average decrease of 1.5 h in time to positivity for each 10-fold increase in concentration; in this study, the time to positivity was significantly shorter for central line blood cultures than for those taken from peripheral sites in patients with CRS [26].

In a retrospective clinical study, we investigated the times to positivity of cultures of blood taken simultaneously from central and peripheral veins to see whether they were different in patients with CRS and patients without [25]. Sixty-four patients were selected for a retrospective analysis of their charts, because cultures of central and peripheral blood taken simultaneously were both positive for the same microorganism. The patients' charts were reviewed by two physicians, who were aware of the type of organisms identified in the blood cultures and in the cultures of the catheters (when available) but were blinded to the time to positivity of the central and peripheral blood cultures. On the basis of criteria derived from those of Raad and Bodey [4], the charts were classified as indicating definite or likely CRS, and refuted or unlikely CRS. The diagnosis and classification were then compared with the differential time to positivity found for the central and peripheral blood cultures. Earlier positivity of central versus peripheral vein blood cultures was shown to be highly predictive of CRS in our population of cancer patients with long-term catheters (median duration of catheter placement 5.5 months; range 1–30 months). The differential time to positivity between central and peripheral blood cultures was significantly greater in patients with CRS (median: 427 min) than in the patients for whom CRS was ruled out or thought unlikely

(median: −15 min; $P<10^{-4}$). A cut-off limit of +120 min had sensitivity and specificity above 95% for the diagnosis of CRS [25].

These results have recently been confirmed by a prospective study in cancer patients with suspected CRS [27]. Using the same cut-off limit of +120 min for the differential time to positivity between central and peripheral blood cultures, a sensitivity of 94% and a specificity of 91% were obtained for the diagnosis of CRS. In addition, useful information may be obtained when the results of paired blood cultures are dissociated, i.e. when a single one of the paired blood cultures is positive, as recently suggested by DesJardin et al. [28]. Positivity of the hub blood culture only may either reflect contamination of the sample or a definite CRS. We suggest that these situations should be viewed as a dynamic process [27]. When such a dissociated pair (catheter positive / venipuncture negative) is recorded first, an additional pair (catheter positive / venipuncture negative or catheter positive / venipuncture positive) usually indicates a CRS. Conversely, if no other positive blood culture is recorded (i.e. only one catheter positive / venipuncture positive pair), this pattern reflects contamination during sampling. This is in agreement with the interpretation of multiple positive blood cultures for distinguishing true bacteraemia and pseudo-bacteraemia due to coagulase-negative staphylococci [29]. When the peripheral blood culture only is positive (catheter negative / venipuncture positive), we are probably facing a true bacteraemia related to another focus of infection, except when skin microorganisms such as coagulase-negative staphylococci are involved [27, 28].

The value of the absolute time to positivity of each blood culture may also be useful. In our study, the median time to positivity of the hub blood culture was significantly shorter in patients with CRS than in other cases, and a time to positivity greater than 24 h excluded a CRS [27]. However, in patients with bacteraemia with coagulase-negative staphylococci, other authors found no difference in the time to detection of positive blood cultures between contaminated samples and true bacteraemia [30, 31].

For an accurate interpretation of the differential time to positivity, we recommend using the first millilitres taken for central blood cultures, without purging the catheter, and taking the same volumes of blood for the CVC and peripheral blood cultures (Table 1). That this new technique is cost-effective seems likely, but this will need to be evaluated by subsequent prospective studies. Indeed, although paired blood cultures are taken, only aerobic bottles are needed. Qualitative blood cultures have been shown to be about half as costly as quantitative blood cultures [7]. In addition, the procedure described here may avoid unjustified removal of the CVC when the differential time to positivity between central and peripheral blood cultures is short, and unjustified prolonged antibiotic treatment when the differential time to positivity is long.

Table 1 Technical recommendations for appropriate use of paired blood cultures. These precautions are essential for adequate interpretation of the results

1	Only aerobic blood cultures are needed
2	The peripheral blood culture, which is often more difficult to draw, should first be performed; it will determine the volume that need to be retrieved for the hub blood culture
3	The same volume (e.g. 5 ml) should be drawn for both catheter and peripheral blood cultures
4	For hub-blood cultures of multilumen catheters, blood should be drawn from the distal port

Our results may be influenced by the particular case-mix of the population studied (most of our patients had long-term catheters). In a preliminary study of differential time to positivity between central and peripheral blood cultures, Mermel et al. reported results with lower sensitivity (73%) and specificity (69%) [32]. That may account for a possible shorter duration of catheterisation in their population of critical care patients. For this reason, a study dedicated to short-term catheters placed in the ICU should be performed to test our results in another setting.

Other techniques for rapid diagnosis of CRS without removing the catheter have been proposed, such as endoluminal brushing of the catheter followed by a microscopic examination of blood samples using an acridine orange leucocyte cytospin (AOLC) test [33, 34]. The latter method was considered as sensitive and specific as quantitative blood cultures for the diagnosis of CRS, but despite encouraging preliminary data the theoretical risk of embolisation or subsequent bacteraemia should be considered. More recently, Kite et al. studied the usefulness of Gram staining and the acridine orange leucocyte cytospin test for rapid diagnosis of CRS without catheter removal [35]. The Gram staining and AOLC test requires two 50-μl samples of catheter blood, treated with edetic acid, vortexing and centrifugation of the cellular suspension, and the use of light and ultraviolet microscopy for examination of a monolayer of leucocytes and microorganisms after acridine orange or Gram staining. The technique is considered simple, rapid (30 min) and inexpensive [35]. A sensitivity of 96%, a specificity of 91%, a negative predictive value of 97% and a positive predictive value of 91% are reported for the diagnosis of bacteraemic CRS in surgical patients. These operational values are similar to those obtained using the measurement of the differential time to positivity [27]. In addition, this method allows a rapid diagnosis and could permit early targetted antimicrobial therapy or, conversely, avoid unnecessary antibiotic use, particularly glycopeptides.

As underlined by Farr, the value of both methods (differential time to positivity, and Gram staining and AOLC test) must be confirmed by other investigators and in other settings before either can be recommended for routine use [36]. Both techniques could be more accurate for long-dwelling catheters, such as those used in cancer patients, than for short-term catheters. This is consistent with the CVC lumen as the predominant source of infection in patients with long-term catheterisation [35]. The easier method to set up immediately would be the differential time to positivity test, given that many clinical microbiology laboratories use continuous monitoring blood culture systems that and many physicians already investigate a new fever by taking simultaneous samples of catheter and venipuncture blood for cultures [36].

Decision-making algorithm

In conclusion, the following *decision-making algorithm* may be proposed for cases of suspected *catheter-related sepsis* [37]:

- If septic shock of undetermined origin is seen in a patient with a CVC, or when local signs of infection (such as purulence or cellulitis) are present, the catheter needs to be removed as a matter of urgency and a quantitative culture of the catheter tip (and eventually of the port) must be performed. Antibiotics should be started immediately.
- When septic shock and local purulence are absent, two types of methods should be implemented simultaneously:
  A technique with high sensitivity and negative predictive value for CRS (skin and hub blood cultures). If both techniques are negative, a CRS can reasonably be excluded.
  A technique with high specificity and positive predictive value for catheter-related bloodstream infection, such as paired blood cultures with measurement of the differential time to positivity between central and peripheral blood cultures. If the latter time is greater than 2 h a CRS is likely. If it is less than 2 h another focus of infection is likely. Gram staining and AOLC test could be also proposed in this setting.
- In the case of persisting suspicion of CRS, a guidewire exchange of the catheter may be performed (if technically possible). If the quantitative culture of the tip of the first catheter is positive, the second catheter should be removed (except in some cases of coagulase-negative staphylococcus infection) and a new catheter placed in another site.

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