EDITORIAL

Conservative methods for diagnosing catheter-associated bacteremia

Métodos conservadores para el diagnóstico de bacteriemia asociada a catéter

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Catheter-associated bacteremia (CAB) is a frequent cause of nosocomial infection in the critical patient\(^{1-4}\) and implies an increase in both morbidity–mortality and healthcare costs.\(^{5-8}\)

The classical method for confirming CAB involves the concomitant isolation of the microorganism in blood cultures obtained by percutaneous puncture and from catheter tip cultures. This conventional procedure has the inconvenience of requiring catheter withdrawal in order to allow tip culture. In this context, there are arguments both in favor and against systematic catheter removal when suspecting CAB. In favor of withdrawal is the fact that many studies have reported a lesser mortality or duration of CAB when the catheter is removed.\(^{9-14}\) However, these studies pose the limitation of having a non-randomized design. In turn, the arguments against catheter withdrawal include: (I) the low yield of systematic catheter tip culture, with positive cultures in under 10% of all cases according to different series\(^{15-17}\); (II) a randomized study has shown that routine catheter removal is not necessary in stable patients.\(^{18}\) The study included patients with suspected CAB, and excluded hemodynamically unstable subjects, immune depressed patients and individuals with signs of local infection. The patients were randomized to either routine catheter removal or catheter maintenance until the blood culture results were obtained. In this latter group catheter removal was decided if blood culture proved positive, if hemodynamic instability developed, or when the suspicion of CAB persisted after 3–5 days. In contrast, in the absence of these circumstances, the catheter was kept in place. There were no differences in patient outcome (in terms of either mortality or the duration of hospital admission) between the two groups, though fewer cases of catheter removal were recorded in the catheter maintenance group; (III) catheter canalization through repeat puncture is subject to mechanical complications such as hemothorax, pneumothorax, vascular dissection, stroke secondary to carotid artery puncture, etc.\(^{19}\)

Therefore, the use of conservative techniques for diagnosing CAB, which allow us to keep the catheter in place, can offer the advantage of avoiding unnecessary catheter withdrawal and the risk of mechanical complications. These conservative methods include the differential time to positivity (DTP) of blood cultures obtained simultaneously through the catheter and by peripheral vein puncture; quantitative differential culture of blood samples collected through the catheter and via the percutaneous route; semi-quantitative superficial cultures of the skin surrounding the catheter insertion point and connections; the staining of blood aspirated through the catheter; endoluminal catheter brushing; and the application of molecular techniques to blood obtained through the catheter.

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shows positive growth at least 120 min before positivity of a blood sample collected at the same time through peripheral vein puncture. The studies that have analyzed DTP have reported a sensitivity of 67–96%, a specificity of 43–100%, a positive predictive value (PPV) of 33–100%, and a negative predictive value (NPV) of 54–99%.\textsuperscript{20–28} In the prospective study carried out by Vallés et al. in critical patients and published in this number of Medicina Intensiva,\textsuperscript{19} the DTP technique showed a sensitivity of 80%, a specificity of 99%, a PPV of 92%, and an NPV of 98%. Previous studies involving short-duration catheterization have documented a sensitivity of 67–96%, a specificity of 43–92%, a PPV of 33–96%, and an NPV of 75–99%.\textsuperscript{24–28} Thus, Vallés et al. recorded higher specificity than in the previous studies, with PPV and NPV values at the upper limit of the previously published ranges. The authors excluded cases of polymicrobial bacteremia, due to the impossibility of determining the DTP of each microorganism, and assumed that this explains the greater specificity recorded in their study (an aspect that had not been taken into account in the previous studies). It is therefore concluded that DTP may be a valid technique for diagnosing monobacterial CAB in critical patients subjected to short-duration catheterization, allowing us to avoid unnecessary catheter withdrawals. Another novel finding is that the authors, in a receiver operating characteristic (ROC) curve, observed that a cutoff point of 20 h in the time to positivity of a blood culture obtained through the catheter can be useful for diagnosing CAB, and that beyond this time the probability of CAB is very low. The DTP technique poses the inconvenience of having to alert the Department of Microbiology to ensure that blood culture incubation is performed immediately upon reception of the sample. Another problem is the difficulty of blood reflow through the catheter lumen in some cases.\textsuperscript{30} On the other hand, in some patients it is difficult to obtain blood cultures through puncture – though a group has attempted to solve this problem by extracting blood cultures through the different catheter lumens. This group assumed the existence of CAB when the difference in blood culture positivity between the different lumens was over 180 min, with a sensitivity of 61% and a specificity of 94%.\textsuperscript{31}

(2) Quantitative differential culture of blood samples. CAB is diagnosed when the colony forming unit (cfu) count of the microorganism per ml in blood obtained through the catheter is at least three-fold greater than the count in the peripheral vein blood sample. The studies that have analyzed this technique have reported a sensitivity of 47–100%, a specificity of 89–100%, a positive predictive value of 63–100%, and a negative predictive value of 78–100%.\textsuperscript{31–42} In the same way as the DTP technique, this method poses the inconvenience of having to alert the Department of Microbiology; blood reflow through the catheter lumen is lacking in some cases;\textsuperscript{30} and in some patients it is not possible to obtain blood cultures through peripheral puncture. Nevertheless, the same group that attempted to overcome this latter problem in the case of the DTP technique also attempted to resolve it in quantitative blood culture. In this context, the group assumed CAB when the quantitative blood culture growth corresponding to one catheter lumen was seen to be at least 5-fold greater than the growth obtained from another lumen—the associated sensitivity being 62%, with a specificity of 93% and a PPV of 92%.\textsuperscript{43} An additional inconvenience is that the resources needed for applying this technique are not widely available.

(3) Semiquantitative superficial cultures (semiquantitative cultures of the skin surrounding the catheter insertion point and connections). A swab is used to rub the skin around the catheter insertion site (1–2 cm in radius), while another swab is used to sweep within the catheter connections, rotating it 2–3 times inside. Both swabs are then quickly cultured. CAB is considered when the same microorganism is found to grow in some of these surface cultures with counts of ≥15 cfu/plate and in peripheral blood. Fortún et al.\textsuperscript{44} reported low sensitivity for isolated insertion site skin and catheter connection cultures (<61%). On combining the superficial cultures, the sensitivity and specificity increased to above 80%, however.\textsuperscript{44–46} A limitation of this technique is that there is no consensus regarding the cutoff point for establishing a diagnosis of CAB; as a result, this technique was not considered in the meta-analysis published by Safdar et al.\textsuperscript{47} In contrast, the advantage of the superficial culture technique is that it is easy to perform and is widely available.

(4) Staining of catheter-aspirated blood. The blood is drawn through the catheter and is treated (with sterile water or hypertonic saline) to cause red cell lysis. The sample is then centrifuged and the supernatant is discarded. Finally, the cell pellet of leukocytes and possible microorganisms is subjected to gram or acridine orange staining. CAB is considered in the presence of positive acridine orange staining in blood collected through the catheter and from peripheral venous puncture. The method is simple, rapid (30–60 min) and inexpensive. Acridine orange staining has yielded a sensitivity of 87–92% and a specificity of 92–97% in diagnosing BAC.\textsuperscript{48–50} Although the technique is simple, experience with its use is still limited.

(5) Endoluminal brushing. This technique involves advancing a brush through a catheter lumen to the vicinity of its distal tip, followed by sweeping of the internal wall to remove the adhered biofilm and microorganisms. The sample is then cultured. CAB is considered in the presence of growth in excess of 100 cfu in the quantitative brush culture. A group in Leeds (United Kingdom) has had good experience with this method, reporting a sensitivity of 95% and a specificity of 84%, with no complications.\textsuperscript{51–53} However, other groups have not obtained such good results.\textsuperscript{54,55} In the study of McLure et al., the sensitivity was found to be 14%, with a specificity of 80%.\textsuperscript{54} Muñoz et al. in turn reported a sensitivity of 30% and a specificity of 95%.\textsuperscript{55} The procedure has some limitations, including the need for different brushes designed to adapt to each type of catheter, and the fact that brush insertion proves difficult in catheters with lateral lumen orifices. Furthermore, it is necessary to calculate the brush segment to be inserted, since arrhythmias may result from atrial stimulation (Muñoz), and there is a risk of embolization and bacteremia.\textsuperscript{56}
Molecular methods. These techniques are based on the detection of nucleic material of the microorganisms. A number of options are available: (1) amplification techniques, including polymerase chain reaction (PCR), ligase chain reaction (LCR), transcription mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), and branched DNA techniques (bDNA); (2) hybridization techniques, including fluorescent in situ hybridization (FISH); (3) microarray techniques capable of identifying multiple pathogens; and (4) protein-based identification techniques involving spectroscopy. The most widely known methods are PCR and FISH. The theoretical advantages of these methods is that they avoid some of the problems of conventional blood cultures, such as the inhibiting effect of antimicrobials, and are moreover rapid (3–6 h). The limitations involved are the difficulty of identifying all the causal microorganisms (only the material of the specific microorganisms investigated is detected); no information is obtained on sensitivity to microbial agents; the techniques are expensive; and they moreover detect any microorganism material in blood—and this does not necessarily mean that the microorganism in question is responsible for the infection (since the material may correspond to dead organisms). Regarding the problem of specificity, the latter has been shown to increase on raising the cutoff point corresponding to the amount of microorganism material in blood, from 93% with a cutoff point of >0.125 pg/μL to 98% with 0.25–0.5 μL and 100% with >0.5 pg/μL.

The problem is that the different conservative methods for diagnosing catheter-associated bacteremia (CAB) have not been compared in one same study. The metaanalysis published by Safdar et al. examined DTP, quantitative differential culture of blood samples and acridine orange staining. The authors concluded that these methods are acceptable, because all of them offer sensitivity and specificity performances of over 75%, though quantitative differential culturing of blood samples was seen to be more reliable. The study of Bouza et al. in turn compared semi-quantitative superficial cultures, quantitative differential culture of blood samples, and DTP. The authors concluded that all three techniques offer high sensitivity (78%, 71% and 96%, respectively), specificity (92%, 97% and 90%, respectively), PPV (61%, 83% and 61%, respectively) and NPV (96%, 95% and 99%, respectively), and finally recommended the use of superficial cultures. In a study carried out by the Leeds group, comparisons were made of DTP, quantitative blood cultures and endoluminal brushing. The authors concluded that all three techniques offer high sensitivity (72%, 89% and 100%, respectively) and specificity (95%, 97% and 89%, respectively), and advocated the use of DTP as first choice technique with a view to preserving the catheter. When blood culturing from the catheter lumen is not possible, the authors recommended endoluminal brushing.

The diagnostic criteria for CAB recommended by the IDSA guidelines published in 2009 are the following: (1) growth of the same organism at the catheter tip (>15 cfu in semi-quantitative culture or >102 cfu in quantitative culture) and in the percutaneous puncture blood sample (level of evidence A-I); (2) growth of the same organism in the cultures of the blood sample collected through the catheter and in the percutaneous puncture blood sample, with compliance of the quantitative blood culture criteria (i.e., the colony count corresponding to the cultures of the blood sample collected through the catheter should be at least three-fold higher than the count corresponding to the puncture blood sample) or DTP criteria (i.e., the growth of microorganisms in the catheter blood samples should be detectable at least 120 min before growth is noted in the puncture blood sample) (A-II); (3) in patients in whom blood cultures cannot be obtained through percutaneous puncture, the diagnosis can be established when quantitative blood culture growth corresponding to the sample obtained through one catheter lumen is at least three times greater than the growth corresponding to another lumen (B-II). However, although a study has been made involving DTP between different catheter lumens, it is suggested that there are no data allowing interpretation of the results in this clinical circumstance (C-III); (4) in long-indwelling catheters, a semiquantitative growth of <15 cfu corresponding to the same organism at the catheter insertion site and in the catheter connections strongly suggests that the catheter is not the origin of bacteremia (A-II). No recommendations are made referred to the molecular techniques, the staining of catheter blood samples, or endoluminal brushing.

In my opinion, further studies are needed to validate the routine use of these conservative methods in diagnosing CAB. However, they could be considered in certain stable and immune competent patients without evidence of local or catheter infection, with a view to avoiding catheter removal. In this context, decision making involves two questions: (1) When should non-removal of the catheter be evaluated? and (2) What method should be used to discard CAB?

The following aspects should be taken into account when deciding whether or not to remove the catheter: (A) the difficulty of creating new accesses in patients with poor vascular access; (B) the possibility of mechanical complications with important clinical consequences, as in patients with coagulation disorders (who are more susceptible to hemothorax or to more abundant hemothorax) or respiratory disease (in which pneumothorax or hemothorax could prove life-threatening); and (C) the possibility that the catheter is effectively the origin of sepsis. In this sense, jugular vein catheters in tracheostomized patients and femoral vein catheters are associated to a higher risk of CAB, while antimicrobial-impregnated catheters may pose a lesser risk of CAB.

In turn, when deciding the diagnostic method to be used, it should be taken into account that the lack of studies simultaneously comparing the different techniques precludes definition of the best option—though the most extensively evaluated techniques have been DTP and quantitative blood cultures (both with acceptable results in terms of sensitivity and specificity). In this sense, the study carried out by Vallés et al. in critical patients suggests that DTP could help reduce unnecessary catheter withdrawal. Those methods requiring blood sampling through the catheter pose the problem that in some cases there is no blood reflow—though this problem does not exist in the case of endoluminal brushing and superficial cultures. Endoluminal brushing has the inconvenience of being expensive and requires the use of material...
adapted to each type of catheter. The problem with superficial cultures in turn is that it may prove difficult to interpret the growth of coagulase-negative staphylococci, which simply may represent contamination. The molecular methods are not affected by the inhibitory action of antimicrobials, but are expensive. The staining of blood samples collected through the catheter is rapid (approximately 30–60 min), but provides no information on the sensitivity to antimicrobial drugs. The molecular techniques are also rapid (3–6 h), but are very expensive. On the other hand, the experience of each individual center in the use of these techniques is of course a very important factor to be taken into account.

In conclusion, the development of methods for diagnosing CAB without the need for catheter removal can contribute to avoid unnecessary catheter withdrawal and lessen the mechanical complications associated to the use of vascular catheters.

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References

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