Med Intensiva. 2012;36(3):163–168

medicina intensiva

www.elsevier.es/medintensiva

EDITORIAL

Conservative methods for diagnosing catheter-associated bacteremia☆

Métodos conservadores para el diagnóstico de bacteriemia asociada a catéter

L. Lorente

Unidad de Cuidados Intensivos, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain

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; semiquantitative 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.

(1) DTP of blood cultures. CAB is diagnosed when the blood sample obtained through any of the catheter lumens

☆ Please cite this article as: Lorente L. Métodos conservadores para el diagnóstico de bacteriemia asociada a catéter. Med Intensiva. 2012;36:163–8.

E-mail address: lorentemartin@msn.com

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%.[20–28] In the prospective study carried out by Vallés et al. in critical patients and published in this number of *Medicina Intensiva*,[29] 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%.[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.[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%.[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%.[32–42] 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[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%.[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 $\geq$15 cfu/plate and in peripheral blood. Fortún et al.[44] reported low sensitivity for isolated insertion site skin and catheter connection cultures ($\leq$61%). On combining the superficial cultures, the sensitivity and specificity increased to above 80%, however.[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.[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.[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.[51–53] However, other groups have not obtained such good results.[54,55] In the study of McLure et al., the sensitivity was found to be 14%, with a specificity of 80%.[54] Muñoz et al. in turn reported a sensitivity of 30% and a specificity of 95%.[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.[56]

(6) 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,[57] 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^{-1} and 100% with >0.5 pg/μL.[58]

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.[47] 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.[24] in turn compared semiquantitative 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,[23] 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[59]: (1) growth of the same organism at the catheter tip (>15 cfu in semiquantitative 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[43] (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[60] and femoral vein catheters are associated to a higher risk of CAB,[61] while antimicrobial-impregnated catheters may pose a lesser risk of CAB.[62–64]

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.[29] 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.

Financial support

This study has been supported by a grant from the *Instituto de Salud Carlos III* (I3SNS-INT-11-063) (Madrid, Spain).

References

1. Alvarez-Lerma F, Palomar M, Olaechea P, Otal JJ, Insausti J, Cerdá E, Grupo de Estudio de Vigilacia de Infección Nosocomial en UCI. Estudio Nacional de Vigilancia de Infección Nosocomial en Unidades de Cuidados Intensivos. Informe evolutivo de los años 2003–2005. Med Intensiva. 2007;31:6–17.
2. Alvarez Lerma F, Olaechea Astigarraga P, Palomar Martínez M, Insausti Ordeñana J, López Pueyo MJ, Grupo de Estudio ENVIN-HELICS. Epidemiología de las bacteriemias primarias y relacionadas con catéteres vasculares en pacientes críticos ingresados en servicios de medicina intensiva. Med Intensiva. 2010;34:437–45.
3. Palomar Martínez M, Alvarez Lerma F, Riera Badía MA, León Gil C, López Pueyo MJ, Díaz Tobajas C, et al., Grupo de Trabajo del Estudio Piloto «Bacteriemia Zero». Prevention of bacteriema related with ICU catheters by multifactorial intervention: a report of the pilot study. Med Intensiva. 2010;34:581–9.
4. Proyecto «Bacteriemia zero». Protocolo de prevención de las bacteriemias relacionadas con catéteres venosos centrales (BRC) en las UCI españolas [accessed 2011 Dec 21]. Available from: http://hws.vhebron.net/bacteriemia-zero/bzero.asp
5. Siempos II, Kopterides P, Tsangaris I, Dimopoulou I, Armaganidis AE. Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta-analysis. Crit Care Med. 2009;37:2283–9.
6. Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis. 2011;11:30–8.
7. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect. 2006;63:124–32.
8. Olaechea PM, Alvarez-Lerma F, Palomar M, Insausti J, López-Pueyo MJ, Martínez-Pellús A, et al., Grupo ENVIN-HELICS. Impact of primary and intravascular catheter-related bacteremia due to coagulase-negative staphylococci in critically ill patients. Med Intensiva. 2011;35:217–25.
9. Lecciones JA, Lee JW, Navarro EE, Witebsky FG, Marshall D, Steinberg SM, et al. Vascular catheter-associated fungemia in patients with cancer: analysis of 155 episodes. Clin Infect Dis. 1992;14:875–83.
10. Rex JH, Bennett JE, Sugar AM, Pappas PG, Serody J, Edwards JE, et al., NIAID Mycoses Study Group and the Candidemia Study Group. Intravascular catheter exchange and duration of candidemia. Clin Infect Dis. 1995;21:994–6.
11. Girmenia C, Martino P, De Bernardis F, Gentile G, Boccanera M, Monaco M, et al. Rising incidence of *Candida parapsilosis fungemia* in patients with hematologic malignancies: clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis. 1996;23:506–14.
12. Nguyen MH, Peacock Jr JE, Tanner DC, Morris AJ, Nguyen ML, Snydman DR, et al. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, prospective, observational study. Arch Intern Med. 1995;155:2429–35.
13. Nucci M, Colombo AL, Silveira F, Richtmann R, Salomão R, Branchini ML, et al. Risk factors for death in patients with candidemia. Infect Control Hosp Epidemiol. 1998;19:846–50.
14. Luzzati R, Amalfitano G, Lazzarini L, Soldani F, Bellino S, Solbiati M, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis. 2000;19:602–7.
15. Widmer AF, Nettleman M, Flint K, Wenzel RP. The clinical impact of culturing central venous catheters. A prospective study. Arch Intern Med. 1992;152:1299–302.
16. Raad II, Sabbagh MF, Rand KH, Sherertz RJ. Quantitative tip culture methods and the diagnosis of central venous catheter-related infections. Diagn Microbiol Infect Dis. 1992;15:13–20.
17. Blackett RL, Bakran A, Bradley JA, Halsall A, Hill GL, McMahon MJ. A prospective study of subclavian vein catheters used exclusively for the purpose of intravenous feeding. Br J Surg. 1978;65:393–5.
18. Rijnders BJ, Peetermans WE, Verwaest C, Wilmer A, Van Wijngaerden E. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med. 2004;30:1073–80.
19. Lorente L, León C. Cateterización venosa femoral: ¿realmente hay que evitarla? Med Intensiva. 2009;33:442–9.
20. Blot F, Schmidt E, Nitenberg G, Tancrède C, Leclercq B, Laplanche A, et al. Earlier positivity of central-venous-versus peripheral-blood cultures is highly predictive of catheter-related sepsis. J Clin Microbiol. 1998;36:105–9.
21. Malgrange VB, Escande MC, Theobald S. Validity of earlier positivity of central venous blood cultures in comparison with peripheral blood cultures for diagnosing catheter-related bacteremia in cancer patients. J Clin Microbiol. 2001;39:274–8.
22. Gaur AH, Flynn PM, Giannini MA, Shenep JL, Hayden RT. Difference in time to detection: a simple method to differentiate catheter-related from non-catheter-related bloodstream infection in immunocompromised pediatric patients. Clin Infect Dis. 2003;37:469–75.
23. Catton JA, Dobbins BM, Kite P, Wood JM, Eastwood K, Sugden S, et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. Crit Care Med. 2005;33:787–91.
24. Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C, Muñoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis. 2007;44:820–6.
25. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med. 2004;140:18–25.
26. Seifert H, Cornely O, Seggewiss K, Decker M, Stefanik D, Wisplinghoff H, et al. 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. J Clin Microbiol. 2003;41: 118–23.
27. Rijnders BJ, Verwaest C. Difference in time to positivity of hub-blood versus nonhub-blood cultures is not useful for the diagnosis of catheter-related bloodstream infection in critically ill patients. Crit Care Med. 2001;29:1399–403.
28. Blot F, Nitenberg G, Chachaty E, Raynard B, Germann N, Antoun S, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. Lancet. 1999;354: 1071–7.
29. García X, Sabatier C, Ferrer R, Fontanals D, Duarte M, Colomina M, et al. Differential time to positivity of blood cultures: a valid method for diagnosing catheter-related bloodstream infection in the Intensive Care Unit. Med Intensiva. 2012;36: 169–76.
30. Sherertz RJ, Heard SO, Raad II. Diagnosis of triple-lumen catheter infection: comparison of roll plate, sonication, and flushing methodologies. J Clin Microbiol. 1997;35:641–6.
31. Gaur AH, Flynn PM, Heine DJ, Giannini MA, Shenep JL, Hayden RT. Diagnosis of catheter-related bloodstream infections among pediatric oncology patients lacking a peripheral culture, using differential time to detection. Pediatr Infect Dis J. 2005;24: 445–9.
32. Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative blood culture. Eur J Clin Microbiol Infect Dis. 1989;8:142–4.
33. Quilici N, Audibert G, Conroy MC, Bollaert PE, Guillemin F, Welfringer P, et al. Differential quantitative blood cultures in the diagnosis of catheter-related sepsis in intensive care units. Clin Infect Dis. 1997;25:1066–70.
34. Capdevila JA, Planes AM, Palomar M, Gasser I, Almirante B, Pahissa A, et al. Value of differential quantitative blood cultures in the diagnosis of catheter-related sepsis. Eur J Clin Microbiol Infect Dis. 1992;11:403–7.
35. Collignon PJ, Soni N, Pearson IY, Woods WP, Munro R, Sorrell TC. Is semiquantitative culture of central vein catheter tips useful in the diagnosis of catheter-associated bacteremia? J Clin Microbiol. 1986;24:532–5.
36. Flynn PM, Shenep JL, Barrett FF. Differential quantitation with a commercial blood culture tube for diagnosis of catheter-related infection. J Clin Microbiol. 1988;26:1045–6.
37. Douard MC, Arlet G, Leverger G, Paulien R, Waintrop C, Clementi E, et al. Quantitative blood cultures for diagnosis and management of catheter-related sepsis in pediatric hematology and oncology patients. Intensive Care Med. 1991;17: 30–5.
38. Douard MC, Clementi E, Arlet G, Marie O, Jacob L, Schremmer B, et al. Negative catheter-tip culture and diagnosis of catheter-related bacteremia. Nutrition. 1994;10:397–404.
39. Mosca R, Curtas S, Forbes B, Meguid MM. The benefits of Isolator cultures in the management of suspected catheter sepsis. Surgery. 1987;102:718–23.
40. Raucher HS, Hyatt AC, Barzilai A, Harris MB, Weiner MA, LeLeiko NS, et al. Quantitative blood cultures in the evaluation of septicemia in children with Broviac catheters. J Pediatr. 1984;104:29–33.
41. Douard MC, Arlet G, Longuet P, Troje C, Rouveau M, Ponscarme D, et al. Diagnosis of venous access port-related infections. Clin Infect Dis. 1999;29:1197–202.
42. Paya CV, Guerra L, Marsh HM, Farnell MB, Washington 2nd J, Thompson RL. Limited usefulness of quantitative culture of blood drawn through the device for diagnosis of intravascular-device-related bacteremia. J Clin Microbiol. 1989;27: 1431–3.
43. Franklin JA, Gaur AH, Shenep JL, Hu XJ, Flynn PM. In situ diagnosis of central venous catheter-related bloodstream infection without peripheral blood culture. Pediatr Infect Dis J. 2004;23:614–8.
44. Fortún J, Perez-Molina JA, Asensio A, Calderón C, Casado JL, Mir N, et al. Semiquantitative culture of subcutaneous segment for conservative diagnosis of intravascular catheter-related infection. JPEN J Parenter Enteral Nutr. 2000;24:210–4.
45. Cercenado E, Ena J, Rodríguez-Créixems M, Romero I, Bouza E. A conservative procedure for the diagnosis of catheter-related infections. Arch Intern Med. 1990;150:1417–20.
46. León M, García M, Herranz MA, González V, Martínez A, Castillo F, et al. Diagnostic value of Gram staining of peri-catheter skin and the connection in the prediction of intravascular-catheter-related bacteremia. Enferm Infecc Microbiol Clin. 1998;16:214–8.
47. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med. 2005;142:451–66.
48. Quintana R, Prieto MF, Bagilet DH, Dalman MC, Gregorini E. Acridine orange staining method in the diagnosis of catheter-related bloodstream infections. Med Intensiva. 2008;32: 168–71.
49. Tighe MJ, Kite P, Thomas D, Fawley WN, McMahon MJ. Rapid diagnosis of catheter-related sepsis using the acridine orange leukocyte cytospin test and an endoluminal brush. JPEN J Parenter Enteral Nutr. 1996;20:215–8.
50. Bong JJ, Kite P, Ammori BJ, Wilcox MH, McMahon MJ. The use of a rapid in situ test in the detection of central venous catheter-related bloodstream infection: a prospective study. JPEN J Parenter Enteral Nutr. 2003;27:146–50.
51. Dobbins BM, Kite P, Catton JA, Wilcox MH, McMahon MJ. In situ endoluminal brushing: a safe technique for the diagnosis of catheter-related bloodstream infection. J Hosp Infect. 2004;58:233–7.
52. Dobbins BM, Catton JA, Kite P, McMahon MJ, Wilcox MH. Each lumen is a potential source of central venous catheter-related bloodstream infection. Crit Care Med. 2003;31: 1688–90.
53. Kite P, Dobbins BM, Wilcox MH, McMahon MJ. Rapid diagnosis of central-venous-catheter-related bloodstream infection without catheter removal. Lancet. 1999;354:1504–7.
54. McLure HA, Juste RN, Thomas ML, Soni N, Roberts AP, Azadian BS. Endoluminal brushing for detection of central venous catheter colonization—a comparison of daily vs. single brushing on removal. J Hosp Infect. 1997;36:313–6.
55. Muñoz P, Llancaqueo A, Cercenado E, Vallejo J, Bouza E. Evaluation of a new endoluminal brush to detect in situ central venous catheter infection. In: VIII Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). 1997. p. 509.
56. Blot F, Nitenberg G, Brun-Buisson C. New tools in diagnosing catheter-related infections. Support Care Cancer. 2000;8:287–92.
57. Kudo M, Matsuo Y, Nakasendo A, Inoue S, Goto H, Tsukiji J, et al. Potential clinical benefit of the in situ hybridization method for the diagnosis of sepsis. J Infect Chemother. 2009;15:23–6.
58. Millar MR, Johnson G, Wilks M, Skinner R, Stoneham S, Pizer B, et al. Molecular diagnosis of vascular access device-associated infection in children being treated for cancer or leukaemia. Clin Microbiol Infect. 2008;14:213–20.
59. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al., Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52:e162–93.
60. Lorente L, Jiménez A, Martín MM, Castedo J, Galván R, García C, et al. Influence of tracheostomy on the incidence of central venous catheter-related bacteremia. Eur J Clin Microbiol Infect Dis. 2009;28:1141–5.

61. Lorente L, Henry C, Martín MM, Jiménez A, Mora ML. Central venous catheter-related infection in a prospective and observational study of 2595 catheters. Crit Care. 2005;9: 631–5.
62. Lorente L, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. The use of rifampicin-miconazole-impregnated catheters reduces the incidence of femoral and jugular catheter-related bacteremia. Clin Infect Dis. 2008;47:1171–5.
63. Lorente L, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. Lower assistance costs using rifampicin-miconazole-impregnated catheters than standard catheters. Am J Infect Control. 2011;39:895–7.
64. Lorente L, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. Rifampicin-miconazole-impregnated catheters save cost in jugular venous sites with tracheostomy. Eur J Clin Microbiol Infect Dis. 2011. December 22 [Epub ahead of print].