Original Article

Is it feasible to diagnose catheter-related candidemia without catheter withdrawal?

Ana Fernández-Cruz1,*, Pablo Martín-Rabadán1,2,3, Marisol Suárez-Salas1, Loreto Rojas-Wettig1, María Jesús Pérez1,3, Jesús Guinea1,3, María Guembe1, Teresa Peláez1,2,3, Carlos Sánchez-Carrillo1 and Emilio Bouza1,2,3 on behalf of the COMIC (Colaboración en Micología) Study Group

1Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain; 2Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Universidad Complutense, Madrid, Spain and 3CIBER de Enfermedades Respiratorias, Palma de Mallorca, Spain

*To whom correspondence should be addressed. E-mail: anafcruz@telefonica.net

This study was previously presented in part at the 52th ICAAC as a Poster (# M-1688); 9–12 September 2012; San Francisco, USA.

Received 17 October 2013; Revised 19 December 2013; Accepted 15 February 2014

Abstract

Many bloodstream infections (BSI) in patients with central venous catheters (CVC) are not catheter-related (CR). Assessment of catheter involvement without catheter withdrawal has not been studied in candidemia. We assessed the value of conservative techniques to evaluate catheters as the origin of candidemia in patients with CVC in a prospective cohort study (superficial Gram stain and culture, Kite technique (Gram stain and culture of the first 1 cm blood drawn from the CVC), proportion of positive blood cultures (PPBCs), differential time to positivity (DTP), and minimal time to positivity (MTP)). All catheters were cultured at withdrawal. From June 2008 to January 2012, 22 cases fulfilled the inclusion criteria. CR-candidemia (CRC) was confirmed in 10. Validity values for predicting CRC were: superficial Gram stain (S, 30%; Sp, 81.83%; PPV, 60%; NPV, 56.3%; Ac, 57.1%), superficial cultures (S, 40%; Sp, 75%; PPV, 57.1%; NPV, 60%; Ac, 59.1%), Kite Gram stain (S, 33.3%; Sp, 66.7%; PPV, 50%; NPV, 50%; Ac, 50%), Kite culture (S, 80%; Sp, 66.7%; PPV, 66.7%; NPV, 80%; Ac, 66.7%), PPBC (S, 50%; Sp, 41.7%; PPV, 41.7%; NPV, 50.0%; Ac, 45.5%), DTP (S, 100%; Sp, 72.7%), and MTTP (S, 70%; Sp, 58.3%; PPV, 58.3%; NPV, 70%; Ac, 63.6%). While combinations of two tests improved sensitivity and NPV, more than two tests did not improve validity values. Classic tests to assess CR-BSI caused by bacteria cannot be reliably used to diagnose CRC. Combinations of tests could be useful, but more and larger studies are required.

Key words: catheter-related bloodstream infection, candidemia, superficial culture.
Introduction

Candidemia is a major health problem. In the last two decades, the incidence of candidemia increased by almost 500% in the United States. Candidemia is the fourth leading cause of bloodstream infection, with a population-based incidence of 10 cases per 100,000 inhabitants [1] and an attributable mortality of 14.5%–50% [2].

Catheter-related candidemia accounts for 35%–80% of all cases of candidemia [3], and withdrawal of the catheter is the recommended strategy for management of the infection [4]. However, many cases are not related to the presence of a catheter. It is important to know if the catheter is the source of candidemia before it is removed. If it is the source of infection, it should be withdrawn immediately because a delay in removal is associated with higher mortality. If the catheter is not the source of infection, it can remain in place, thus preventing future complications.

Catheter-related candidemia is usually confirmed by means of catheter culture. To our knowledge, it is not possible to predict catheter infection prior to withdrawal of the device [5]. Several techniques for predicting catheter-related bacteremia without catheter withdrawal have been proposed [6–9], although most have not been validated specifically for candidemia. A recent retrospective study by our group in which we compared three techniques in patients with candidemia showed disappointing results [10].

Here, we prospectively evaluated the performance of five methods for predicting catheter-related candidemia. Our objective was to find a method that could rule out the central venous catheter (CVC) as the source of infection while in situ in order to optimize management and avoid unnecessary withdrawal.

Materials and methods

Our institution is a 1550-bed tertiary teaching hospital that served a reference population 650,000 to 750,000 during the study period. The hospital is a referral center with active major heart surgery and transplantation programs as well as a cooperative multidisciplinary group for the prospective study of mycoses.

Study period and patient selection

Since 1997, the microbiology and infectious diseases service has systematically followed all patients with bloodstream infections (including fungemia) contracted and treated at our institution. This enabled us to evaluate all patients who had candidemia during the period June 2008 through January 2012. We prospectively enrolled adult patients with blood cultures growing Candida and a CVC in situ at evaluation. All patients enrolled gave their consent to participate, and the local ethics committee approved the study. We obtained samples from catheter hubs and the skin surrounding the insertion site for Gram staining and culture (superficial samples), samples of the first 1 cm of fluid from the catheter (Kite technique) for Gram staining and culture, and differential blood cultures drawn from the catheter hub. Peripheral vein puncture was performed in order to measure differential time to positivity (DTP; if the index blood culture was not already a differential blood culture). We also studied the proportion (>1/2 or ≥2/3) of positive blood cultures (PPBCs). We recommended withdrawal of the catheter after sample collection, and all catheters were cultured (tip, port, or both) to confirm or exclude catheter-related candidemia.

Sample collection and microbiological methods

Blood cultures

Blood cultures were obtained using standard procedures. Samples taken through 2009 were processed using the BACTEC 9240 (Becton Dickinson, Sparks, MD, USA) and those taken from 2010 through 2012 were processed using the BACTEC FX (Becton Dickinson). All testing was performed according to the manufacturer’s instructions. When the blood culture was positive and the Gram stain demonstrated the presence of a yeast, a subculture was performed in CHROMagar (CHROMagar Candida, Paris, France). The yeasts were identified by ID32 (bioMérieux, Marcy L’Étoile, France), and antifungal susceptibility was determined by microdilution method (Sensititre YeastOne; Trek Diagnostic Systems LTD, West Sussex, England).

Superficial cultures

Superficial samples for Gram staining and culture were obtained from catheter hubs and skin. The skin samples were obtained by lifting the dressing and rubbing the area around the insertion site (3-cm radius) with a dry cotton swab. The inner hub samples were obtained using alginate swabs that were introduced into the hub and rubbed repeatedly against its inner surface (one swab per hub). All swabs were semi-quantitatively processed immediately by streaking the entire surface of Columbia agar plates supplemented with 5% sheep’s blood. The plates were incubated aerobically for 72 h at 35°C, and the recovered colonies were counted.

Kite technique

The first 1 cm of fluid from the catheter was drawn without purging to perform a Gram stain after removal of hemoglobin. Next, 100 µL was plated on Columbia blood agar and in CHROMagar for culture [7].
Proportion of positive blood cultures
We assessed the number of peripheral blood cultures obtained and those that turned positive. A cutoff of ≥2 positive results out of ≥2 blood cultures from the same sample was considered suggestive of catheter origin [10].

DTP
We simultaneously drew 10 ml of blood from each hub and from a peripheral vein to ascertain DTP using conventional blood cultures. All blood culture bottles were taken immediately to the microbiology laboratory and placed in an automatic culture detector (BACTEC 9240 or BACTEC FX; Becton Dickinson), which recorded CO₂ readings every 15 min. Catheter-related candidemia was defined as growth of the same microorganism from a blood sample drawn through a catheter hub at least 2 h earlier than the positivity of the blood sample obtained from the peripheral vein [11].

Minimal time to positivity
Minimal time to positivity (MTP) was defined as the time elapsed from the introduction of peripheral blood cultures into the incubating machine to the moment the first bottle turned positive with Candida species. Candidemia was considered catheter related when MTP was below a cutoff of 30 h [6].

Catheter tip culture
The catheter tip sample was taken after scrubbing the skin surrounding the insertion site with 2% chlorhexidine and cutting off the tip (distal 5-cm segment) using sterile scissors. The catheter tip was cultured using the semiquantitative roll-plate technique [12] and according to Infectious Diseases Society of America guidelines. Culture-negative tips were longitudinally sectioned and rubbed on the surface of a blood agar plate. We considered the culture to be positive if any number of yeast colony-forming units (CFUs; qualitative criterion) were present.

Catheter port culture
Port content aspirate was obtained before sonication. The whole port was then sonicated for 1 min and vortexed for 15 s. Next, the saline used for the port sonication and port content aspirate after sonication was cultured. Last, the port silicone membrane was opened using a punch, and a sterile swab was rubbed on the internal surface for qualitative culture [13].

Clinical criteria and definitions
We defined an episode of candidemia as the isolation of Candida from one or more blood cultures. Cases with only one positive blood culture were also included, even if the culture was the one drawn from a catheter hub. We considered candidemia to be catheter related when the same Candida (genus and species) was isolated from both the catheter tip or port by means of a qualitative culture and at least one blood culture. We considered candidemia to be noncatheter related when culture of the catheter tip and port was sterile or showed a microorganism other than the yeast recovered in blood culture.

We recorded the following clinical data: age, sex, underlying disease, microbiological etiology, length of hospital stay, length of intensive care unit stay, type of catheter, number of catheter lumens, insertion site, and indwelling time. We also evaluated patients for other possible sources of candidemia, therapy with antifungal agents, and outcome.

Statistical analysis
We compared the effectiveness of the five techniques in predicting catheter-related candidemia. The reference standard was a positive result for a conventional blood culture and a qualitative catheter tip or port culture result that was positive for the same microorganism. Cases with and without confirmed catheter-related candidemia were compared. Associations between variables were evaluated using the χ² test for categorical variables, the t test for normally distributed continuous variables, and the Mann–Whitney test for nonparametric comparisons. A P value <0.05 was considered significant. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for each test and for combinations of tests. The statistical analysis was performed with SPSS 16.0 (SPSS, Chicago, IL, USA).

Results
From June 2008 through January 2012, we recorded 320 episodes of yeast fungemia involving 260 patients. Of these, 50 had a CVC in situ at evaluation. Children were not included. Twenty-seven episodes were excluded because the sample set was not complete. One episode was excluded because it was caused by Trichosporon. The final sample comprised 22 episodes, fulfilling the inclusion criteria. After the analysis, 10 had confirmed catheter-related candidemia and the remainder had noncatheter-related candidemia.

Table 1 shows the characteristics of the 22 episodes according to origin. When we compared the clinical characteristics of the population and the catheters, we could not find any significant differences between confirmed catheter-related candidemia and nonconfirmed episodes. Of note, in half of the cases included, the catheter was not withdrawn.
Table 1. Demographic and clinical data for 22 episodes of candidemia in patients with a central venous catheter.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Catheter related (10)</th>
<th>Noncatheter related (12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>5/5</td>
<td>8/4</td>
<td>0.666</td>
</tr>
<tr>
<td>Age, y (median, IQR)</td>
<td>66 (53–77)</td>
<td>68 (44–72)</td>
<td>1</td>
</tr>
<tr>
<td>Kind of catheter</td>
<td></td>
<td></td>
<td>0.302</td>
</tr>
<tr>
<td>• Central venous nontunneled</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>• Tunneled</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>• Totally implantable</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Catheter use</td>
<td></td>
<td></td>
<td>0.949</td>
</tr>
<tr>
<td>• Total parenteral nutrition</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Chemotherapy</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>• Hemodialysis</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Catheter insertion site</td>
<td></td>
<td></td>
<td>0.467</td>
</tr>
<tr>
<td>• Internal jugular vein</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>• Subclavian vein</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>• Femoral vein</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of lumens (days, median, IQR)</td>
<td>2.5 (1–3)</td>
<td>2 (2–3)</td>
<td>1</td>
</tr>
<tr>
<td>Length of use (days, median, IQR)</td>
<td>25 (17–45)</td>
<td>39 (11–149)</td>
<td>0.670</td>
</tr>
<tr>
<td>Time on antifungals before withdrawal (median, IQR)</td>
<td>3 (0.75–5.25)</td>
<td>6 (1–10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Species of fungus</td>
<td></td>
<td></td>
<td>0.334</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>3*</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other Candida</td>
<td>3*</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Alternative source of candidemia</td>
<td>3</td>
<td>5</td>
<td>0.675</td>
</tr>
<tr>
<td>Proportion of positive BC/total BC</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1/2 or 1/3</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>&gt;1/2 or 1/3</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Differential time to positivity &gt;120</td>
<td>10</td>
<td>8</td>
<td>0.096</td>
</tr>
<tr>
<td>Time differential (median, IQR)</td>
<td>22 (11–28)</td>
<td>27 (17–53)</td>
<td>0.656</td>
</tr>
</tbody>
</table>

BC, blood culture; IQR, interquartile range.
*Mixed candidemia: 1 C. albicans and 1 C. pelliculosa, 1 C. albicans and 1 C. krusei.

immediately but remained in place with antifungal therapy for a median of 5 days. Candida parapsilosis was found only among confirmed cases of catheter-related candidemia.

The results of the tests for each episode are summarized in Table 2. Among cases with confirmed catheter-related candidemia, one had only one positive test result. Catheter culture was sterile in 12 of the 22 cases. Among cases with a sterile catheter, one had positive results in all five tests; that patient had received 39 days of antifungal therapy prior to withdrawal.

Table 3 shows a comparison of the validity values from the five conservative techniques for the diagnosis of catheter-related candidemia. DTP was the most sensitive technique (100%), and superficial Gram staining had the greatest specificity (81.8%). In particular, except for DTP, negative predictive values were all <85%.

Combinations of tests were analyzed in order to evaluate whether their performance exceeded that of individual tests. Table 4 shows the comparison of validity values of combined tests. Combinations of two tests improved sensitivity and negative predictive value. Combinations of more than two tests did not improve validity values.

**Discussion**

Our results suggest that no individual noninvasive test is sufficiently reliable to rule out the catheter as the source of candidemia. Combinations of tests could increase accuracy, although their performance is still insufficient to rule out the catheter as the source of candidemia.

Catheter-related candidemia is an increasingly common health problem. Withdrawal is beneficial when the catheter is confirmed as the source of candidemia, although this approach is not without complications. Other studies have shown the usefulness of noninvasive techniques for identifying the source of bloodstream infection in patients with...
Table 2. Results of different tests performed for 22 episodes of candidemia.

<table>
<thead>
<tr>
<th>Number of Confirmed episodes</th>
<th>Number of Qualitative cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>1/1  Yes  Male  80  22 CVC  3  0  C. albicans 1/1 CRP 13 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/1  Yes  Female 76  22 CVC  3  1  C. albicans 1/2 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/2  Yes  Male 76  6 CVC  3  5  C. albicans 1/2 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/2  Yes  Female 74  15 CVC  3  1  C. glabrata 1/2 CRP 12 CVC 15 C. glabrata</td>
<td>Positive</td>
</tr>
<tr>
<td>1/2  Yes  Male 76  6 CVC  3  5  C. albicans 1/2 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/1  No  Male 70  11 CVC  3  1  C. albicans 1/2 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/1  No  Female 77  234 Port 1  14  C. albicans 1/4 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
<tr>
<td>1/1  No  Female 77  234 Port 1  14  C. albicans 1/4 CRP 12 CVC 15 C. albicans</td>
<td>Positive</td>
</tr>
</tbody>
</table>

BC, blood culture; CRC, catheter-related candidemia; CVC, central venous catheter.
a CVC [5,7–9]. Previously, we found a high negative predictive value of superficial cultures for ruling out catheter-related bacterial bloodstream infection [14]. In that study, only 6 of 29 episodes of catheter-related bloodstream infection were caused by fungi.

Few studies have focused on candidemia. Ben-Ami et al. suggested that a time to positivity for blood cultures of <30 h was associated with catheter origin [6]. Recently we reviewed retrospective data and did not find an optimal test for prediction of catheter-related candidemia from among MTP of blood cultures, DTP, and number of positive blood cultures, although the proportion of positive blood cultures showed a high negative predictive value for ruling out the catheter as the source of candidemia [10].

Our results do not validate the favorable results obtained for bacteremia; it is possible that the slower growth of fungi could alter time to positivity. Furthermore, it has not been established whether the standard cutoff of 2 h for bacteremia is adequate for fungi. In our study, DTP showed good sensitivity and negative predictive values, at the expense of low specificity and positive predictive value. In addition, we cannot exclude the possibility that the sensitivity of DTP was falsely increased by the inclusion of patients with only one positive culture drawn from the catheter lumen. Consequently, DTP results should be interpreted with caution. It is also possible that the proportion of catheter-related bacteremia in patients with suspected catheter-related bacteremia and a CVC (28/204; 13.7%) [14] is

<table>
<thead>
<tr>
<th>Table 3. Values of tests used to predict source of candidemia as the catheter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>Superficial Gram</td>
</tr>
<tr>
<td>Superficial culture</td>
</tr>
<tr>
<td>Superficial</td>
</tr>
<tr>
<td>Kite Gram</td>
</tr>
<tr>
<td>Kite culture</td>
</tr>
<tr>
<td>Kite</td>
</tr>
<tr>
<td>Differential time to positivity</td>
</tr>
<tr>
<td>Minimal time to positivity</td>
</tr>
<tr>
<td>Proportion of positive ≥2</td>
</tr>
</tbody>
</table>

*Candidemia was considered catheter related when minimal time to positivity was below a cutoff of 30 h.

**A cutoff of ≥2 positive results out of ≥2 blood cultures from the same sample was considered suggestive of catheter origin.

<table>
<thead>
<tr>
<th>Table 4. Values of test combinations of used to predict source of candidemia as the catheter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>DTP + SUP</td>
</tr>
<tr>
<td>DTP + Kite</td>
</tr>
<tr>
<td>DTP + PPBC</td>
</tr>
<tr>
<td>SUP + Kite</td>
</tr>
<tr>
<td>SUP + PPBC</td>
</tr>
<tr>
<td>KITE + PPBC</td>
</tr>
<tr>
<td>MTP + SUP</td>
</tr>
<tr>
<td>MTP + Kite</td>
</tr>
<tr>
<td>MTP + PPBC</td>
</tr>
<tr>
<td>MTP + DTP</td>
</tr>
<tr>
<td>DTP + SUP + Kite</td>
</tr>
<tr>
<td>DTP + SUP + PPBC</td>
</tr>
<tr>
<td>DTP + SUP + MTP</td>
</tr>
<tr>
<td>DTP + MTP + Kite</td>
</tr>
<tr>
<td>DTP + MTP + PPBC</td>
</tr>
<tr>
<td>DTP + PPBC + Kite</td>
</tr>
<tr>
<td>SUP + Kite + MTP</td>
</tr>
<tr>
<td>SUP + Kite + PPBC</td>
</tr>
<tr>
<td>SUP + MTP + PPBC</td>
</tr>
</tbody>
</table>

DTP, differential time to positivity; SUP, superficial culture; PPBC, proportion of positive blood cultures; MTP, minimal time to positivity.
much lower than the proportion of catheter-related candidemia in patients with candidemia and a CVC (67/108, 62%), thus making it difficult to find a test with a high negative predictive value.

Our results do not validate those obtained retrospectively by our group [10], which ruled out cases with catheter culture and only 1–14 CFU Candida per plate, although the number of colony-forming units needed to confirm that a catheter is the cause of infection is not well defined for Candida. Cases where only the blood culture obtained through the catheter was positive (usually considered catheter colonization) were also excluded in that study. Only two cases of totally implantable catheters were included, although candidemia is often found in patients with this type of catheter. Finally, only cases with a catheter tip cultured within 7 days after diagnosis of candidemia were included. Since it often takes longer to remove a permanent catheter, we cannot exclude the possibility that some catheter-related cases were missed. Even when we recalculated our figures based on those criteria, the values did not improve (data not shown).

The present study is subject to limitations. We could not include a considerable number of cases whose catheters were already withdrawn when the blood culture became positive, nor did we include cases whose catheters were not finally withdrawn. Therefore, our data may underestimate the real incidence of catheter origin in patients with candidemia. Moreover, in half of the cases included, the catheter was not withdrawn immediately but remained in place with antifungal therapy for a median of 5 days, thus potentially altering the result of blood cultures, catheter cultures, and, in particular, time to positivity.

Based on our results, we cannot recommend individual classic tests for evaluating catheter-related bloodstream infection to exclude catheter-related candidemia before catheter withdrawal. Combinations of tests could be useful, but more and larger studies are required.

Acknowledgments

We are grateful to Thomas O’Boyle for editorial assistance.

Funding

This study was financed by grants from Fundación Mutua Madrileña de Madrid. This study was supported by the Ministerio de Sanidad y Consumo (Instituto de Salud Carlos III) and Fundación para la Investigación Biomédica del Hospital General Gregorio Marañón (FIBHGM) (CM09/00028). PROMULGA Project. Instituto de Salud Carlos III. PI1002868

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References