Letter to the Editor

Limitations of Semiquantitative Method for Catheter Culture

We have read with much interest the study of Collignon et al. (2) and its discussion by Bruni Buisson et al. (C. Bruni Buisson, A. Rauss, and P. Legrand, Letter, J. Clin. Microbiol. 25:1343–1344, 1987). We feel that the major cause of disagreement between these groups is to be found in the inherent limitations of the semiquantitative method (SQM) for catheter-tip culture. It is the purpose of this letter to call attention to three insufficiencies of the SQM while at the same time clarifying some confusion existing in the literature concerning the relationship between bacteremia and the results of the SQM.

(i) The positive predictive value of the SQM is proportional to the mean catheterization time. The association between positive SQM (15 CFU) and catheter-related sepsis (CRS) differs from one study to another. We have analyzed the positive predictive value of the SQM of tips of central venous catheters (positive SQM with bacteremia/all positive SQM × 100) in five reports (2, 4–7). We found that the frequency with which a positive SQM of the tip is linked to bacteremia ranges from 8 to 45% and that there seems to exist a fairly good correlation between mean catheter placement time and the percentage of positive SQM which were associated with CRS (Table 1). These findings imply that some time elapses between bacterial contamination able to produce a positive SQM and the clinical expression of the colonized catheter through bacteremia. The microbiological events that take place during this period, as well as its duration, await further elucidation.

(ii) Catheter sepsis with negative SQM. We reported (3) that the SQM yielded false-negative results in 2 of 14 cases of CRS originating at the catheter hub. In such circumstances the tip becomes colonized by endoluminal bacterial migration, and bacterial growth on the outer catheter surface may not be prominent. In these cases, the SQM, on the basis of cultures of the external surface of the catheter tip, may yield fewer than 15 CFU. Collignon et al. (2) also reported two false-negative results in 13 cases of CRS. Thus, when the SQM is used, no growth or growth of less than 15 CFU should not dismiss the catheter as the cause of bacteremia. We agree with Bruni Buisson et al. (Letter, J. Clin. Microbiol.) that lowering the dividing line to 5 CFU only increases the number of false-negative results and offers no substantial advantage in terms of diagnosing bacteremia. Instead, other culture methods should be used as a complement to the SQM, particularly if CRS is suspected. Because false-negative results can be obtained in bacteremias related to endoluminal catheter contamination, hub cultures should be routinely used (3, 8). A negative SQM would not prevent the clinician from diagnosing CRS in cases in which the same microorganism is recovered from the blood and the catheter hub. Also, the quantitative method of Cleri et al. (1) could eventually replace the SQM, because it cultures both the inner and outer surfaces of the catheter tip and is theoretically more sensitive than the SQM.

(iii) The catheter needs to be removed to make the diagnosis of catheter sepsis. Leaving aside the cases in which there is an obvious infection of the skin entry site, the clinician most often faces the problem of fever of unknown origin in a patient with one or more intravenous catheters which he is reluctant to replace. An approach that may give the diagno-

Table 1. Relationship between positivity of the SQM and some clinical variables

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cultures</th>
<th>Mean placement time (days)</th>
<th>No. (%) of positive SQM cultures</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinilla et al. (6)</td>
<td>291</td>
<td>3.5</td>
<td>28 (8)</td>
<td>12</td>
</tr>
<tr>
<td>Collignon et al. (2)</td>
<td>780</td>
<td>5.5</td>
<td>148 (19)</td>
<td>8.8</td>
</tr>
<tr>
<td>Maki et al. (4)</td>
<td>250</td>
<td>10</td>
<td>25 (10)</td>
<td>16</td>
</tr>
<tr>
<td>Moyer et al. (5)</td>
<td>101</td>
<td>10</td>
<td>28 (28)</td>
<td>20</td>
</tr>
<tr>
<td>Sherertz et al. (7)</td>
<td>60</td>
<td>19</td>
<td>22 (37)</td>
<td>45</td>
</tr>
<tr>
<td>Our series</td>
<td>200</td>
<td>24</td>
<td>40 (20)</td>
<td>75</td>
</tr>
</tbody>
</table>

* Positive SQM associated with bacteremia.

s of CRS before the line is withdrawn is to perform a Gram stain and a culture of the inner surface of the catheter hub with a swab. This new diagnostic tool has proved useful in selected patients of our own and should be used to identify catheters infected through the hub route.

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Authors' Replies

Drs. Sitges-Serra and Liñares make some interesting comments on the possible limitations of the semiquantitative culture (SQC) technique designed by Maki et al. (8) and propose one explanation for a possible lack of sensitivity of the SQC technique to diagnose catheter-related sepsis (CRS) or bacteremia. In our opinion, the major problem with the SQC technique is that it was designed to diagnose significant colonization (not specifically infection) of catheter tips while eliminating the bulk of contaminated catheters. There was a limited attempt in the series by Maki to correlate microbiologic findings (i.e., colonization) with clinical sepsis (local inflammation at the skin insertion site was the major clinical parameter assessed), and the very small number of catheter-related bacteremias in this study rendered the cutoff limit of 15 CFU/ml rather arbitrary (4). This results in significant lack of specificity (i.e., a high number of false-positive results) of the technique for the diagnosis of infection (5), while its sensitivity is probably satisfactory. In fact, most studies, including those by Collignon et al. and Cooper and Hopkins (4–6), show that, irrespective of catheterization duration, only 5 to 30% of catheters defined as colonized by the SQC technique can lead to CRS and/or bacteremia, making this approach useful for epidemiologic purposes but not optimal for clinical diagnostic purposes.

The first comment by Sitges-Serra and Liñares is related to the duration of catheterization and positive predictive value of a positive SQC: the longer a catheter remains intravascular, the more likely is a positive SQC to be associated with CRS and bacteremia. Most studies on this subject, including ours (2), have shown a correlation between duration of catheterization and incidence of CRS. This suggestion that a colonized catheter remaining intravascular can eventually lead to overt infection and/or bacteremia is also logical. The consequence is that the routine use of the quantitative technique becomes debatable when most positive catheters, examined by both quantitative and nonquantitative techniques, are associated with infection (9).

As emphasized by Sitges-Serra and Liñares, CRS with "negative" (i.e., fewer than 15 CFU) SQC has been documented in several studies (5, 6), including those by Collignon et al., which lead us to adapt the technique of Cleri et al. (3) for routine use in the microbiology laboratory, as suggested by Sitges-Serra and Liñares; we found this simplified quantitative technique to be of high sensitivity and specificity (both over 80%) for diagnosis of CRS, whether bacteremic or not (2). Sitges-Serra and Liñares suggest that most of the false-negative SQC are due to infection via the hub (7), which leads to colonization of the internal lumen of the catheter, occasionally undetected by the "roll-on-agar" technique of Maki et al. (8). However, the hub route probably does not account for all false-negative SQCs, since large numbers of organisms have been demonstrated by Gram staining of catheters on both their internal and external surfaces, while SQCs are negative (4, 6). Thus, technical problems could also account in part for these negative SQCs.

Finally, Sitges-Serra and Liñares address the difficult and still unresolved problem of diagnosing CRS before the intravenous line is removed. While a definitive diagnosis can be obtained only by Gram stain and/or culture of the incriminated intravenous line, this objective is of obvious interest for the patient with difficult and continued need for vascular access. Several approaches have been proposed for this purpose, including routine cultures of the cutaneous entry site of the catheter (11), SQCs of blood drawn through the catheter (9), and now Gram stain and culture of the inner surface of the hub, as suggested by Sitges-Serra and Liñares. However, blood cultures drawn through the catheter can be positive due to skin insertion site—or possibly hub—colonization in the absence of significant growth from the intravascular segment (10). I caution against hub cultures as the sole means for diagnosing CRS. Besides, skin-insertion-site colonization is in most studies the major route of catheter colonization (1–11). Obviously, none of these techniques is entirely satisfactory; each of them is directed at detecting one of the possible mechanisms of CRS.

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However, we think it is misleading to discuss positive predictive values (PPV) without commenting on the prevalence of disease, as this will affect the PPV. A test of excellent sensitivity and specificity, such as the enzyme-linked immunosorbent assay for human immunodeficiency virus, has a very low PPV when used on a population of low disease prevalence (e.g., community blood donors). With any test, the higher the prevalence of disease, the higher will be the PPV. The prevalence of catheter sepsis is closely associated with the length of time a catheter has been in situ (2, 5). Thus, no matter what test is used, a higher PPV will be obtained in series in which catheters have been in place for longer periods of time.

A factor which should be taken into account is that central lines behave quite differently from peripheral vein catheters (2) and therefore should not be compared to them, as has been done in Table 1 in the letter of Drs. Sitges-Serra and Liñares. We have redrafted their table, deleting the two studies which were not principally of central vein catheters (8, 10) and adding the prevalence of disease as a separate column (Table 1). As can be seen, the PPV is closely related to the prevalence of catheter-related bacteremia in the population.

With regard to their second point, we have shown that by lowering the cutoff from 15 to 5 CFU we saw an increase in sensitivity with no loss of specificity in our patient population (3). That is, we diagnosed more patients with catheter-associated bacteremia with little increase in the number of false-positive results. Dr. Brun Buisson et al. (C. Brun Buisson, A. Rauss, and P. Legrand, Letter, J. Clin. Microbiol. 25:1343–1344, 1987) recommended raising our cutoff to 100 CFU. If this was done the test would have diagnosed only 38% of the catheter-related bacteremic episodes in our study (an unacceptable result). We are surprised that Drs. Liñares and Sitges-Serra agree with this comment, as in five of the cases of catheter-associated bacteremia in their series (6) semiquantitative culture of catheter tips was associated with counts of less than 100 CFU.

There is no consensus on the pathogenesis of catheter-associated sepsis. In particular, there is doubt whether in most catheter-associated sepsis organisms migrate down the outside of the catheter (Maki [7]) or whether the migration is intraluminal (Liñares et al. [6]). Our own experience with Gram staining impression smears of the external surface of catheters (1) and that of Cooper and Hopkins (4) suggest that the external migration theory is more likely to be correct. In particular, in the study of Cooper and Hopkins, in all cases in which organisms were seen inside the catheter, larger numbers of organisms were seen on the outside of the catheter. The two studies mentioned above show that one reason the numbers of organisms are cultured at times is that many organisms seen on staining are apparently neither nonculturable nor nonviable.

Their third point relates closely to the above discussion on pathogenesis and cannot be adequately addressed until the question of pathogenesis has finally been settled. More research is obviously required. We agree that it would be preferable to have a rapid diagnosis of central vein catheter sepsis without having to remove the catheter. However, we do not believe that there is an appropriate method available that has been proven to be able to do this. We continue to recommend that in a septic patient with an intravascular catheter in place the catheter be removed and cultured unless another site of sepsis can be identified confidently as the cause of the sepsis.

**TABLE 1. Relationship between positivity of semiquantitative catheter culture method and some clinical variables**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of catheters cultured</th>
<th>Mean placement time (days)</th>
<th>Prevalence of catheter-associated sepsis (%)</th>
<th>PPV (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collignon et al. (3)</td>
<td>780</td>
<td>5.5</td>
<td>2</td>
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<tr>
<td>Moyer et al. (9)</td>
<td>101</td>
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</tr>
<tr>
<td>Sherertz et al. (11)</td>
<td>60</td>
<td>19</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>Liñares et al. (6)</td>
<td>135</td>
<td>24</td>
<td>14.8</td>
<td>72</td>
</tr>
</tbody>
</table>

a Percentage of catheters positive by the semiquantitative method which were associated with bacteremia.

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