Catheter-Tip Colonization as a Surrogate End Point in Clinical Studies on Catheter-Related Bloodstream Infection: How Strong Is the Evidence?

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In clinical trials, the incidence of catheter-tip colonization (CTC) is frequently used as a surrogate end point for the incidence of catheter-related bloodstream infection (BSI). It is not clear whether the correlation between CTC and catheter-related BSI is good. We searched the MEDLINE database and conducted a literature search for the years 1990–2002 and retrieved 29 studies (with a total of 60 study groups) with incidence data on predefined CTC and catheter-related BSI definitions. A good linear correlation between CTC and catheter-related BSI was found ($r = 0.69$; $r^2 = 0.48$; $P < .001$). The data from the medical literature about catheter-related infection seem to support the use of CTC as a surrogate end point for catheter-related BSI. In evaluations of clinical interventions or new techniques for the prevention of catheter-related BSI, investigation of the prevention of CTC seems to be a logical first step.

In clinical studies, a surrogate end point for the clinical end point in question is frequently used. For some clinical end points, in cases in which the event studied is relatively rare, extremely large studies would be needed to draw statistically sound conclusions. This is one of the reasons why surrogate end points are used. To illustrate this, imagine an adequately powered ($\alpha = 0.05$; power, 80%; one-sided) clinical study that examines whether sterile barrier precautions undertaken during insertion of an arterial catheter will reduce the incidence of arterial catheter-related bloodstream infection (BSI) by 33% (a clinically relevant reduction). With an estimated rate of catheter-related BSI in the control arm of 5 infections per 1000 catheter-days [1] and a realistic dropout rate of 20% during the study, 2 groups of 9000 catheter-days each would be required. If these catheters stayed in place for an average of 1 week, the study would have to include 2 groups with 1285 catheter placements each. Such megastudies are rarely performed when no commercial interest exists in the particular field of research.

In clinical studies on the prevention of catheter-related infections, catheter-tip colonization (CTC) is frequently used as a surrogate end point for the most severe form of catheter-related infection, catheter-related BSI [2–6]. Use of this end point is based on observations that, in bacteremic patients who have an intravascular catheter in place, the catheter is more likely to be the source of bacteremia if culture of the catheter tip yields the same bacteria as blood culture. The higher the load of bacteria found on the catheter, the better the positive predictive value for catheter-related bacteremia [7–9]. More recently—and for prac-
tical reasons—in most studies of catheter-related infection, an absolute cutoff value for catheter culture positivity has been used.

In this systematic review of the literature, we tried to determine how well CTC performs as a surrogate end point for catheter-related BSI. We did this by analyzing the correlation between the incidence densities (expressed as the number of positive catheter-tip cultures per 1000 catheter-days) for CTC and catheter-related BSI. For this purpose, we reviewed every study group from all published studies (both observational studies and randomized, controlled trials) of catheter-related BSI conducted during January 1990–January 2002 that fulfilled predefined inclusion criteria.

METHODS

An extensive search of the English-language literature was performed by use of the MEDLINE database with the search string “catheter AND infection NOT urinary,” with the limits “clinical trial,” “English,” and “human,” for reports published during January 1990–January 2002. We also checked the Cochrane Library and references from available review reports about catheter-related infections. Posters and presentations that were only available from conference reports were not reviewed, because the presented information was rarely sufficient for the purposes of our study. Only studies (both observational studies and randomized, controlled trials) that involved short-term central venous catheter placements that provided information about CTC and catheter-related BSI (sometimes called “catheter-related sepsis”) were eligible for further inspection; we excluded studies or study group data that involved totally implanted and tunneled catheters. CTC and catheter-related BSI had to be directly or indirectly expressed as events per 1000 catheter-days in the full report. Because CTC and catheter-related BSI rarely were expressed as events per 1000 catheter-days in reports published before 1990, such reports were not reviewed.

The intention to culture all removed catheter tips had to have been indicated in the report, and a semiquantitative (e.g., Maki roll with ≥15 cfu/catheter-tip as a cutoff) or quantitative (e.g., sonication or vortex with 1000 cfu/catheter-tip as a cutoff) catheter-tip culture had to have been used for this purpose [7, 10]. We chose to use only these 2 catheter-tip culture cutoffs, because we wanted to collect a relatively homogenous group of studies and because they were by far the most frequently used cutoffs in the studies reviewed. Because there was no uniform definition of catheter-related BSI used in the literature, we chose to include all studies that provided incidence data about catheter-related BSI, regardless of the definition used; however, a catheter-tip culture (with the aforementioned cut-offs) and ≥1 culture of a blood sample obtained before removal of the catheter had to yield the same phenotypic strain.

By use of the least-squares regression method, a regression line was fitted to the scatter plot of the collected data on CTC and catheter-related BSI for each study group. Ninety-five percent prediction intervals for the regression line were calculated. A residual plot and a normal P-P plot for regression-standardized residuals were used to analyze residuals. The strength of the linear relationship was measured by use of Spearman’s ρ correlation for nonparametric data. P values for the correlation were 2 tailed. SPSS, version 11.0 for Windows (SPSS), was used for statistical calculations.

RESULTS

The first MEDLINE search using the search string “catheter AND infection NOT urinary” yielded 397 hits (figure 1). Three hundred forty-eight of the 397 hits had to be excluded from the study for the following reasons: the report was about peritoneal dialysis catheters (n = 45), the report was about tunneled or totally implanted catheters (n = 44), the report was about oncological or hematological topics and not about catheter-related infection (n = 30), CTC and catheter-related BSI were not mentioned in the abstract (n = 29), the report was about peripheral intravascular catheters (n = 17), the report was about catheters used in neurology or neurosurgery settings (n = 16), the report was about cardiological or radiological procedures (n = 14), or the report was about a topic (e.g., epidural catheters and hemodynamic monitoring in the intensive care unit) other than catheter-related infection (n = 153).

Forty-nine reports remained as possible sources of information for our study. We found 4 additional reports that were possibly useful by checking the reference lists of the reviewed reports about catheter-related BSI (figure 1). Of these 53 reports, 24 were excluded for the reasons mentioned in table 1. We were finally able to collect 29 reports (with a total of 60 study groups) that provided the information on CTC and catheter-related BSI necessary for our analysis [3–5, 32–55]. In total, these 60 study groups had information on 1281 colonized catheters and 259 catheter-related BSIs, for a total of 94,595 catheter-days. The mean CTC and catheter-related BSI incidences were 13.5 events per 1000 catheter-days and 2.7 events per 1000 catheter-days, respectively.

We found good linear correlation between CTC and catheter-related BSI (r = 0.69; r² = 0.48; incidence of catheter-related BSI = 0.73 + 0.17 × incidence of CTC). This correlation was statistically significant (P < .001; figure 2). Residuals were randomly distributed in the residual plot.
DISCUSSION

The aim of this study was to explore the scientific evidence that allows for the use of CTC as a surrogate end point for catheter-related BSI in clinical studies. In the studies that used a quantitative or semiquantitative cutoff criterion for CTC and \( \geq 1 \) blood culture that yielded the same phenotypic strain as the criterion for catheter-related BSI, we found good correlation between CTC and catheter-related BSI in an analysis of data from an extensive literature review. Although we intentionally restricted the analysis to a relatively homogenous group of reports about catheter-related infection, there are several reasons why we found a less-than-perfect correlation. As discussed in Methods, 2 catheter-tip culture methods were allowed for the purposes of this study. Forty-eight study groups used only the Maki-roll catheter-tip culture method, 8 used a quantitative culture method, and the other 4 used a combination of both. This is probably one of the reasons why the correlation we found between CTC and catheter-related BSI is good but not perfect.

Another reason for the suboptimal correlation between CTC and catheter-related BSI is the difference in definitions of catheter-related BSI used in the various studies. There are many definitions of catheter-related BSI used in the literature about catheter-related infection. In large epidemiological studies, the definitions used are frequently easier to implement, because few clinical data are needed. These definitions

<table>
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<tr>
<th>Reason for exclusion</th>
<th>Excluded reference(s)</th>
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<tr>
<td>Data on rate of colonization per 1000 catheter-days was not present</td>
<td>[11–19]</td>
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<tr>
<td>Data on rate of colonization per 1000 catheter-days was not present and catheter-tip culture method was not defined</td>
<td>[20]</td>
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<tr>
<td>Data on rate of colonization per 1000 catheter-days was not present and catheter-related BSI was treated without catheter removal</td>
<td>[21]</td>
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<td>No data on catheter-related BSI</td>
<td>[2, 22–27]</td>
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<td>Cutoff ( \geq 100 \text{ cfu/catheter tip} ) vs. ( 1000 \text{ cfu/catheter tip} )</td>
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<tr>
<td>Catheter-tip culture method not defined</td>
<td>[29]</td>
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<td>Other cutoffs for catheter culture used</td>
<td>[14, 30]</td>
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<td>Data for CVCs not separated from data for all catheters</td>
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NOTE. Catheter-related BSI is defined as a catheter-tip culture that yielded the same phenotypic strain as \( \geq 1 \) culture of a blood sample obtained before catheter removal. CVC, central venous catheter.
are probably more sensitive but less specific. In studies that use more-sensitive definitions, a higher incidence of catheter-related BSI for the same CTC incidence can be expected. The use of different definitions in the studies reviewed in our analysis will logically lead to a decrease in the correlation between CTC and catheter-related BSI.

Furthermore, catheters are made of or coated with many different materials (e.g., polyurethane, silicone, and fluorinated ethylene propylene polymers). The risk of catheter-related BSI for a given level of colonization may differ for the different materials.

Finally, the CTC and catheter-related BSI data used for the analysis involved infections with gram-positive or gram-negative bacteria and yeasts. Although, currently, the same cutoff points for CTC are used for all of these different organisms, a certain degree of CTC due to *Staphylococcus aureus* or *Candida* species may have a stronger predisposition to catheter-related BSI than would the same level of CTC due to *Staphylococcus epidermidis* [9]. This would increase the slope of the regression line for CTC and catheter-related BSI due to *S. aureus* and *Candida* species versus CTC due to *S. epidermidis*. Therefore, notwithstanding of all these limitations, we still demonstrated that there is a good correlation between CTC and catheter-related BSI.

The evidence in the medical literature about catheter-related infection seems to support use of CTC as a surrogate end point for catheter-related BSI. In evaluating new techniques for the prevention of catheter-related BSI, investigation of the prevention of CTC seems to be a logical first step. Also, CTC should be useful to simplify the evaluation of clinical interventions (e.g., the promotion and teaching of hand washing hygiene) aimed at reducing the incidence of catheter-related BSI.

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**References**

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