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Diagnosis of Vascular Catheter-Related Bloodstream Infection: a Meta-Analysis

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Catheter-related bloodstream infections increased in incidence during the past decade, causing significant morbidity, mortality, and excess hospital costs. Absence of inflammation at the catheter site in most cases makes clinical diagnosis uncertain. The relative accuracy and cost-effectiveness of different microbiologic tests for confirming that bloodstream infection is catheter related have remained unclear. A meta-analysis of published studies was conducted regarding the accuracy of diagnostic test methods using pooled sensitivity and specificity and summary receiver operating characteristic (ROC) curve analysis. The cost for each test was estimated by methods published by the College of American Pathologists. Costs of catheter replacement and antibiotic therapy for false positive results were included in the cost per accurate test result. Twenty-two studies evaluating six test methods met inclusion criteria for the meta-analysis. Accuracy increased in ROC analysis for catheter segment cultures with increasing quantitation ($P = 0.03$) (i.e., quantitative > semiquantitative > qualitative) largely due to an increase in specificity. The highest Youden index (mean = 0.85) was observed with quantitative catheter segment culture, the only method with pooled sensitivity and specificity above 90%. For blood culture methods, there was no statistically significant trend toward increased accuracy. The unpaired quantitative catheter blood culture offered the lowest cost per accurate test result but was only 78% sensitive. In conclusion, quantitative culture was the most accurate method for catheter segment culture, and unpaired quantitative catheter blood culture was the single most cost-effective test, especially for long-term catheters.

The incidence of primary nosocomial bloodstream infection increased two- to threefold during the 1980s (4). Much of this increase has been attributed to catheter infection, which causes morbidity, mortality, and excess hospital costs. The excess hospital cost associated with nosocomial bloodstream infection in surviving intensive-care patients in a recent study was $40,000 per patient (64). The case fatality rate for catheter-related bloodstream infection has been estimated to be 10 to 20% (50).

More than 90% of catheter-related bloodstream infections are associated with central venous catheters (52), and the diagnosis of these infections can be difficult (63, 95). Inflammation at the catheter site is not always due to infection, and such local signs are absent in 70% of central venous catheter-related bloodstream infections (63). Although this infection is usually manifested by onset of new fever in an intensive-care unit patient, 80 to 90% of such fevers are not due to catheter infection (17, 24, 79, 87). It has been estimated that 75 to 85% of catheters are removed unnecessarily during evaluation of new fever (79).

Sixteen diagnostic methods and 17 variations have been proposed for laboratory diagnosis of catheter-related bloodstream infection (see Table 1) (1, 6–8, 11, 13, 20–22, 28, 29, 34, 40, 41, 45, 46, 53, 58, 62, 65, 72, 75, 78, 81, 84, 86, 89, 91, 98, 99), but the relative accuracy and cost-effectiveness of these methods have remained unclear. We have conducted a meta-analysis of published studies regarding the accuracy of methods for diagnosing catheter-related bloodstream infection.

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MATERIALS AND METHODS

The English-language medical literature for the years 1966 to 1994 was searched by using Medline for articles about techniques for the diagnosis of vascular catheter-related infections. Review articles, textbook chapters, and references in Medline were also searched. Studies focusing upon evaluation of methods for diagnosis of catheter-related infection were included. Studies primarily addressing risk factors, management, or prevention of catheter-related infection were excluded. All studies were reviewed by at least two authors, and decisions regarding exclusion were made by consensus of the authors.

Test methods were grouped into three principal categories: catheter segment culture, culture of blood drawn through the catheter, and a group of miscellaneous methods.

Definitions. Culture methods were defined as qualitative when colonies were not counted, as semiquantitative when specimens were cultured directly and colonies were counted on agar plates allowing enumeration within a limited range only, and as quantitative when serial dilutions of original specimens were used for culture, allowing more precise enumeration (Table 1). Blood culture methods were classified as "unpaired" when only blood aspirated from the catheter was used and as "paired" when concurrent blood cultures were taken from peripheral veins for comparison with blood cultures drawn from the catheter. Sensitivity was defined as the proportion of catheter-related bloodstream infection cases with a positive test, and specificity was defined as the proportion of cases without catheter-related bloodstream infection with a negative test (31).

Catheter-related bloodstream infection was defined in most studies included in the meta-analysis by (i) the presence of clinical features of bloodstream infection, (ii) growth of the same organism from peripheral blood and either a catheter segment or a blood culture aspirated from the catheter, and (iii) the absence of any other possible source for the infection. Four additional studies were evaluated which used the same definition except that the catheter segment culture being studied was excluded from the definition to avoid incorporation bias; one of these studies evaluated qualitative catheter segment cultures (59), and three evaluated semiquantitative catheter segment cultures (20, 21, 58).

Studies which focused upon diagnoses other than catheter-related bloodstream infections and those which did not clearly state their "gold standard" were

TABLE 1. Review of methods for diagnosing catheter-related infection

First author and year	Material employed	Technique	Criterion for positive result	Catheter in situ	Rapid
Druskin (28) 1963	Catheter segment	**Qualitative culture** in broth	Any growth	No	No
Seligman (81) 1974	Catheter segment	**Quantitative culture**		No	No
		Flushing with needle (81)	$\geq 10^3$ CFU per segment		
		Vigorous agitation (7)	$\geq 10^3$ CFU per segment		
		Sonicating (6)	$\geq 10^2$ CFU per segment		
		Vortexing (11)	$\geq 10^3$ CFU per segment		
		Sonicating and vortexing (84)	$\geq 10^2$ CFU per segment		
		Dilutions onto agar, Ultrasonicating (46), and mixing with mole	$\geq 10^2$ CFU per segment		
Maki (53) 1977	Catheter segment	**Semiquantitative** culture on roll plate	≥15 CFU per segment (53) ≥5 CFU per segment (21)	No	No
Wing (98) 1979	Blood from catheter	**Paired quantitative** pour plate **blood** cultures from catheter and peripheral vein	Catheter counts > vein counts (98) Catheter counts > vein counts by 30 (62) Catheter:vein = 7:1 (29) Catheter:vein = 4:1 (13)	Yes Yes No Yes	No
Powell-Tuck (65) 1979	Skin swab insertion site	**Nonquantitative culture** on agar (with every dressing change)	Any growth	Yes	No
Powell-Tuck (65) 1979	Skin swab insertion site	**Gram stain** (if purulent)	Not stated (65)	Yes	Yes
Bjornson (7) 1982	Skin swab at entry site	**Quantitative culture** by dilution plate count after vigorous agitation on blood agar (75)	$\geq 10^3$ CFU per swab (9) ≥5 CFU per swab (75)	No	No
Snydman (89) 1982	Blood from catheter	**Quantitative culture** on pour plate	Any growth (89) ≥25 CFU per ml (58) ≥15 CFU per ml (91) $\geq 10^3$ CFU per ml (1)	Yes No Yes Yes	No
		On solid agar (72)	Any growth (72)	Yes	
Grabe (34) 1983	Inner surface of cannula	**Semiquantitative** roll plate **culture** of steel stiletto inserted into lumen and drawn back and forth	Counts given; no cutoff mentioned	No	No
		Plastic obturator (41)	As above	Yes	No
Grabe (34) 1983	Washing fluid of cannula	**Semiquantitative culture** of centrifuged deposit from washings through sideport and infusion port	As above	No	No
Jakobsen (40) 1983	Inner surface of sideport	**Nonquantitative culture** of a stick rubbed into the inside of the sideport and spread on agar	Any growth	No	No
Bozzetti (8) 1984	Blood from catheter	**Nonquantitative culture** in broth	Any growth	No	No
Sitges-Serra (86) 1984	Catheter hub	**Quantitative culture** flushing with a needle dilution onto agar	$\geq 10^3$ CFU per segment	No	No
Cooper (22) 1985	Catheter segment	**Direct staining**		No	Yes
		Gram stain of catheter segment (23)	≥1 organism per 20 oil immersion fields (22)		
		Gram stain of impression smear of catheter segment (21)	Results given for various levels of counting (21)		
		Acridine orange stain of catheter (99)	Presence of bacteria or fungi (99)		
Rushforth (78) 1993	Blood from catheter	**Acridine orange staining** of monolayered leukocytes from pellet examining with UV microscope	Presence of bacteria	Yes	Yes
Khardori (45) 1993	Catheter segment	**Culture** of tiny sections of catheter embedded into agar	Probably any growth	No	No

excluded. Only studies supplying primary data and using epidemiologic study methods similar enough to be statistically grouped by diagnostic test method were included in the meta-analysis.

Statistical methods. Sensitivity and specificity were computed from the primary data of each study. Two methods were used as summary statistics for comparison of the diagnostic accuracy among tests.

(i) Estimates of sensitivity and specificity. Sensitivity and specificity for each diagnostic test were computed by simple pooling of the primary data from individual studies. The chi-square test for homogeneity in binomial proportions for contingency tables was used to assess variability among the different study results for a particular diagnostic method (76). Fisher's exact test was used for contingency tables in which an expected value was less than 5 (76). The Youden index (sensitivity + specificity − 1) was used as a summary statistical criterion for test performance. Linear regression was used to assess whether there was a trend toward higher mean Youden index values with increasing quantitation of catheter segment cultures (qualitative, semiquantitative, and quantitative) and with increasing quantitation of blood cultures drawn from the catheter (qualitative, unpaired, quantitative, and paired quantitative) (76).

(ii) ROC curve analysis. Pooling sensitivity and specificity separately ignores the fact that both of them depend on the cutoff value used to define a positive test; a stricter cutoff will increase specificity but decrease sensitivity. Summary receiver operating characteristic (ROC) analysis was performed to distinguish variation in decision threshold from actual differences in accuracy as follows. The results of studies evaluating a specific test method were plotted as true positive rates (sensitivity) against false positive rates (1 − specificity) in an ROC space (39, 48, 57, 82). In these plots, a single point represented the two estimated parameters (sensitivity and specificity) from each study. False positive rates and true positive rates were transformed to their logits, U and V, respectively, after increasing each observed frequency by 0.5 (57). For each study, the difference (D) and the sum (S) of the logits were calculated as follows: $D = V - U$; $S = V + U$ (57). The points (S_i, D_i) were plotted for each group of studies and a least-squares simple regression line was fitted by using a linear model, $D = a + bS$ (31). D is the log-odds ratio, a measure of accuracy, whereas S is a function of the decision criterion. A summary ROC curve was then plotted from the regression line by transforming the values back into ROC space by using the estimated parameters a and b for each group of studies (48, 57). The mean D value was used as a basic summary statistical measure of test performance. The Breslow-Day test (10) of homogeneity of odds ratios was used to test the hypothesis that $B = 0$, and the Kardaun-Kardaun test (44) was used to assess the adequacy of the summary ROC curve. Linear regression was used to assess whether there was a trend towards higher mean D values (both unadjusted and adjusted to a common test threshold) with increasing quantitation for catheter segment cultures as well as for blood culture methods (31, 48, 57). All statistical tests were performed by using SAS, SPSS/PC Plus, or S-PLUS software (5, 33, 80).

Methods for estimating cost-effectiveness of diagnostic tests. The total hospital laboratory cost for each diagnostic test method was estimated including costs for personnel, minutes of test time, supplies and reagents, equipment maintenance, logging specimens into the system, computer support, and laboratory overhead. The College of American Pathologists Workload Recording method was used for determination of time needed to complete each microbiological procedure (18). The cost to the entire hospital for each accurate test result was estimated for each test method by using the cost of the test and the pooled sensitivity and specificity for the test. This calculation included assumptions that the prevalence of catheter-related bloodstream infection was 10% among febrile patients, that two sets of peripheral blood cultures would be drawn for each patient, and that patients with false positive test results for blood cultures drawn from the catheter would receive antibiotic therapy. Since a majority of false positive results involve skin flora, especially coagulase-negative staphylococci, and since usual therapy has been 1 to 2 weeks for such infection, the cost estimate included the cost of administering vancomycin for an average of 10 days for false positive blood cultures. The cost for measurement of serum vancomycin concentrations was not included because of recent data suggesting that monitoring these levels increases the cost of care without improving safety or efficacy (12). For the purpose of making this calculation, the costs of a replacement, nontunneled central venous catheter ($88), chest radiograph ($71), and coagulation studies ($47) were included for every patient having catheter segment cultures for diagnosis and for 10% of patients with blood cultures drawn from the catheter (69). No costs were added for infectious complications related to false negative tests or to delay in catheter removal because of blood cultures being drawn through the catheter, as it was assumed that such complications probably occur in less than 0.1% of febrile episodes in catheterized patients.

RESULTS

A total of 156 articles were identified for possible inclusion in the meta-analysis. Of these, 73 focused upon evaluation of diagnostic methods. Ten of these were review articles which did not supply original data (15, 19, 36, 42, 54, 60, 66, 71, 85, 95) and 63 were clinical studies assessing diagnostic methods (Table 2) (2, 3, 9, 14, 16, 23, 25–27, 30, 32, 35, 37, 38, 43, 47, 49, 51, 55, 56, 59, 61, 67, 68, 70, 73, 74, 77, 83, 88, 90, 92–94, 96, 97). Twenty-eight articles supplied primary data with comparison to catheter-related bloodstream infection. Twenty-two of these were similar enough to be statistically combined within six test method groups including three types of catheter segment culture methods (qualitative, semiquantitative, and quantitative) and three blood culture methods (unpaired qualitative catheter blood culture, unpaired quantitative catheter blood culture, and paired quantitative catheter blood culture). These 22 studies are displayed in bold type in Table 2. Articles describing comparisons of multiple test methods are cited more than once in Table 2. Of the six remaining studies, five evaluated various direct staining methods that could not be pooled due to differences in technique (21, 22, 55, 78, 99) and one assessed catheter site skin culture and hub culture (30).

Comparison of sensitivity and specificity. The sensitivity and specificity of the individual test methods with their pooled estimates are displayed in Table 3. Within-group variability was statistically significant ($P < 0.05$) for most test methods except for sensitivity of two of the methods; these results were not altered by inclusion or exclusion of the four studies which sought to avoid incorporation bias by not using the catheter culture being studied as part of their gold standard (20, 21, 58, 59). Sample size was small even after pooling for the two culture methods that had no significant differences in sensitivity among studies. Specificity was heterogeneous for all six methods, so the pooled estimates must be viewed with caution.

The highest pooled sensitivity for a single test method was observed with the qualitative catheter segment culture, and the lowest was with the unpaired quantitative catheter blood culture (Table 3). The highest specificity was observed with the unpaired quantitative catheter blood culture, and the lowest was with the qualitative catheter segment culture. Catheter segment cultures as a group had higher sensitivity and lower specificity compared with the blood culture methods as a group. The highest accuracy in the Youden index was observed with the quantitative catheter segment culture method, and the lowest was with the qualitative catheter segment culture (Table 4). Linear regression analysis of Youden index values suggested a trend toward greater accuracy of catheter segment cultures with increasing quantitation (qualitative, semiquantitative, and quantitative), but this was not statistically significant ($P = 0.065$). No such trend was apparent for blood culture methods ($P = 0.822$).

Comparison among studies by ROC analysis. A scatter plot of the 13 studies evaluating the semiquantitative catheter segment culture and the corresponding ROC curve are shown in Fig. 1, which illustrates the ROC method. The convergence of the 13 individual primary data points into a summary ROC curve is evident. ROC curves for five of the six test methods under comparison are shown in Fig. 2. The four points for the paired quantitative catheter blood culture method did not converge into an appropriate curve. The curves generated and the area under the curves for the qualitative and semiquantitative catheter segment culture methods were not changed significantly when the four studies which sought to avoid incorporation bias by excluding the catheter culture being studied from their gold standard (20, 21, 58, 59) were excluded from the ROC analysis. The curves shown in Fig. 1 and 2 included these four studies.

The ROC curves for the catheter segment cultures lie closer to the upper left corner of the ROC plot, indicating higher accuracy as quantitation increases (Fig. 2); much of the increase in accuracy appears to be due to increased specificity. For the two unpaired blood culture tests, the trend is less

pronounced; the quantitative test appears to increase specificity at the expense of decreased sensitivity. The Kardaun-Kardaun test of homogeneity indicated possible lack of fit of the summary ROC curve only for the unpaired quantitative blood culture ($P = 0.06$); P values for the other methods exceeded 0.33, indicating no detectable heterogeneity with respect to the summary ROC curve.

Statistical comparison of the mean D value among the six culture methods is shown in Table 4. Comparison of mean D values adjusted for threshold did not change the results, so we only presented the unadjusted D values in Table 4. The highest mean D value was observed with the paired quantitative catheter blood culture method followed by the quantitative catheter segment culture method. Linear regression detected a significant increase in accuracy of catheter segment cultures with increasing quantitation ($P = 0.03$) but not with blood culture methods ($P = 0.40$).

Other methods. The five direct staining methods used either gram stain or acridine orange stain of the catheter segment, an impression smear from the catheter segment, a smear of exudate from the catheter skin entry site, or blood leukocytes. As mentioned above, these techniques were not similar enough to be pooled. Their median sensitivity was 87% (range, 60 to 100%), and their median specificity was 88% (range, 64 to 94%).

Cost. The estimated costs for the various tests are shown in Table 5. The highest laboratory cost was associated with paired quantitative blood cultures followed by the quantitative catheter segment culture. The least expensive test was qualitative culture of blood drawn from the catheter.

The test with the lowest cost to the entire hospital per accurate test result was the unpaired quantitative catheter blood culture. Among catheter segment cultures, the semiquantitative method was most cost-effective.

Laboratory costs for direct staining methods were rather low, ranging from $21.94 to $47.27. The cost per accurate test result was not calculated because of the lack of confirmatory studies for each of these methods.

DISCUSSION

Which test is best for diagnosing catheter-related bloodstream infection has remained controversial despite many studies of the question. Most studies have evaluated only 1 or 2 of the 16 proposed methods, leaving the relative accuracy of the different methods unclear. Seligman first proposed the use of quantitative culture of the catheter segment in 1974 (81). Several years later, Maki et al. demonstrated that semiquantitative catheter segment culture was more accurate than qualitative culture of the catheter (53).

The results of this meta-analysis confirmed the superiority of quantitative techniques for catheter segment cultures. Quantitative catheter segment culture was the most accurate method, being the only one with pooled sensitivity and specificity above 90%. It also had the highest Youden index, a method for evaluating diagnostic accuracy which includes an algebraic assumption that sensitivity and specificity of a test are equally important. ROC curves have been advocated as a better means for comparing the accuracy of diagnostic tests than the above parameters because they demonstrate how accuracy varies with both sensitivity and specificity. The marked variability in sensitivity and specificity for each of the methods shows that there is no single sensitivity or specificity for a given test method and, in different studies, illustrates why ROC curves may offer a better comparison of the accuracy of different diagnostic tests (31, 48, 57). The ROC curve for quantitative catheter segment

TABLE 2. Summary of all reported studies evaluating test methods for the diagnosis of catheter-related infections and the respective gold standards[a]

Test method evaluated	Gold standard					Other or unspecified
	Clinical definition		Catheter segment culture			
	Catheter-related bloodstream infection	Catheter-related infection	Qualitative	Semiquantitative	Quantitative	
Catheter segment cultures						
Qualitative	**16, 43, 51, 53, 59**	37, 45, 51			97	56
Semiquantitative	**3, 14, 20–22, 35, 43, 51, 53, 58, 70, 89, 96,** 25, 47, 68, 74, 75, 86	14, 23, 37, 43, 45, 46, 51, 53, 70	51, 53		97	83
Quantitative	**7, 11, 16, 35, 70**, 47, 68, 74, 75, 84, 86	11, 46, 70		70		83
Blood culture from catheter						
Unpaired qualitative	**8, 13, 58, 62, 72, 89**		90			
Unpaired quantitative	**13, 58, 62, 72, 89**			1, 89, 91, 92		
Paired with peripheral vein	**8, 13, 27, 62**			13, 29, 62	27, 38	26, 32, 77, 83, 93, 94, 98
Other methods						
Direct staining	**21, 22, 55, 78, 99**			21–23, 55, 99		65
Insertion site skin swab	30, 47, 86	37, 67	9	2, 30, 41, 49, 55, 61, 67, 88	30, 49, 67, 73	65, 75, 93
Miscellaneous[b]	30, 47, 86	45		34, 41	97	40, 75, 93

[a] Numbers indicate reference numbers; boldface type indicates studies included in the meta-analysis.
[b] Culture of interior surface of cannula, hub culture, or cut-section method.

TABLE 3. Accuracy of test methods for diagnosing catheter-related bloodstream infection

Study	Criterion for positive result	Sensitivity (%)	Specificity (%)
Qualitative catheter segment culture			
Maki et al. 1977 (53)		4/4 (100)	209/246 (85)
Maki et al. 1977 (51)		5/5 (100)	24/45 (53)
Cleri et al. 1980 (16)		13/13 (100)	103/136 (76)
Jones et al. 1986 (43)		12/12 (100)	268/367 (73)
Nahass and Weinstein 1990 (59)		5/7 (71)	48/73 (66)
P value for homogeneity		0.07	<0.001
Pooled estimate		39/41 (95)	652/867 (75)
Semiquantitative catheter culture			
Maki et al. 1977 (53)		4/4 (100)	225/246 (91)
Maki et al. 1977 (51)		5/5 (100)	34/45 (75)
Snydman et al. 1982 (89)		5/5 (100)	63/70 (90)
Moyer et al. 1983 (58)		5/5 (100)	53/68 (78)
Cooper and Hopkins 1985 (22)		12/12 (100)	289/318 (91)
Collignon et al. 1986 (20)		11/13 (85)	610/732 (83)
Jones et al. 1986 (43)		7/12 (58)	342/367 (93)
Collignon et al. 1987 (21)		5/10 (50)	271/312 (87)
Cercenado et al. 1990 (14)		17/18 (94)	85/121 (53)
Aufweber et al. 1991 (3)		15/17 (88)	403/525 (77)
Raad et al. 1992 (70)		8/9 (89)	96/111 (86)
Gutierrez et al. 1992 (35)		10/12 (84)	72/86 (83)
Widmer et al. 1992 (96)		5/6 (83)	145/151 (96)
P value for homogeneity		<0.001	<0.001
Pooled estimate		109/128 (85)	2,688/3,152 (85)
Quantitative catheter segment culture			
Cleri et al. 1980 (16)[a]	$\geq 10^3$ CFU	13/13 (100)	125/136 (92)
Bjornson et al. 1982 (7)[b]	$\geq 10^3$ CFU	8/10 (80)	60/64 (94)
Brun-Bruisson et al. 1987 (11)[c]	$\geq 10^3$ CFU	20/20 (100)	291/311 (94)
Raad et al. 1992 (70)[d]	$\geq 10^2$ CFU	13/14 (93)	72/77 (94)
Gutierrez et al. 1992 (35)[e]		11/12 (92)	72/86 (84)
P value for homogeneity		0.123	<0.03
Pooled estimate		65/69 (94)	620/674 (92)
Unpaired qualitative catheter blood culture method			
Snydman et al. 1982 (89)	Any growth	2/5 (40)	87/95 (91)
Moyer et al. 1983 (58)	≥25 CFU	4/5 (80)	58/62 (92)
Raucher et al. 1984 (72)	Any growth	9/9 (100)	107/128 (84)
Capdevila et al. 1992 (13)	>100 CFU	17/17 (100)	80/90 (89)
Bozzetti et al. 1984 (8)	Any growth	7/8 (87.5)	213/248 (86)
Paya et al. 1989 (62)	Any growth	15/15 (100)	25/37 (68)
P value for homogeneity		<0.001	<0.001
Pooled estimate		54/59 (91)	569/660 (86)
Unpaired quantitative catheter blood culture method			
Snydman et al. 1982 (89)	≥15 CFU	1/5 (20)	90/95 (95)
Moyer et al. 1983 (58)	≥25 CFU	4/5 (80)	62/62 (100)
Raucher et al. 1984 (72)	>100 CFU	9/9 (100)	123/128 (96)
Paya et al. 1989 (62)	>100 CFU	12/15 (80)	31/37 (84)
Capdevila et al. 1992 (13)	>100 CFU	14/17 (82)	89/90 (99)
P value for homogeneity		0.02	<0.001
Pooled estimate		40/51 (78)	395/412 (96)
Paired quantitative blood culture methods			
Raucher et al. 1984 (72)	c/p > 5:1[f]	5/5 (100)	21/21 (100)
Paya et al. 1989 (62)	c−p ≥ 30 CFU	7/15 (47)	27/37 (73)
Douard et al. 1991 (27)	c/p ≥ 3:1	30/36 (83)	22/22 (100)
Capdevila et al. 1992 (13)	c:p ≥ 4:1	16/17 (94)	90/90 (100)
P value for homogeneity		<0.001	<0.001
Pooled estimate		58/73 (79)	160/170 (94)

[a] Flushing used as technique in culture preparation.
[b] Agitating used as technique in culture preparation.
[c] Vortexing used as technique in culture preparation.
[d] Sonicating used as techniques in culture preparation.
[e] Flushing and vortexing used as techniques in culture preparation.
[f] c, concentration in central blood; p, concentration in peripheral blood.

TABLE 4. Summary statistics for comparison of six techniques for the diagnosis of catheter-related bloodstream infection

Method	No. of studies	ROC analysis (mean D value)	Mean Youden index
Catheter segment culture			
Qualitative	5	3.30	0.65
Semiquantitative	13	3.61	0.70
Quantitative	5	4.86	0.85
P value (trend)		0.03	0.065
Blood culture from catheter			
Unpaired qualitative	6	3.86	0.70
Unpaired quantitative	5	4.41	0.67
Paired quantitative	4	4.98[a]	0.74
P value (trend)		0.40	0.82

[a] This value must be interpreted cautiously because three of the studies found very high accuracy (D = 6.16, 5.35, or 7.60) but one reported much lower accuracy (D = 0.84).

cultures included more area under the curve than any other catheter segment culture technique. Linear regression detected a statistically significant increase in accuracy with increasing quantitation of the method (31, 48, 58). While it is plausible that the greater accuracy of this method may derive merely from quantitation, it also may be related to the variable pathogenesis of catheter-related bloodstream infection, which can arise from luminal or extraluminal infection. Quantitative catheter segment culture permits detection of bacteria from either surface of the catheter, whereas the semiquantitative technique detects organisms only on the external surface. For blood cultures aspirated from catheters there was a trend toward greater accuracy with the more quantitative techniques, but this was not statistically significant.

A large recent study of diagnostic methods, excluded from this review because primary data were not available, corroborated the results of the meta-analysis by concluding that quantitative catheter segment culture was the most accurate of

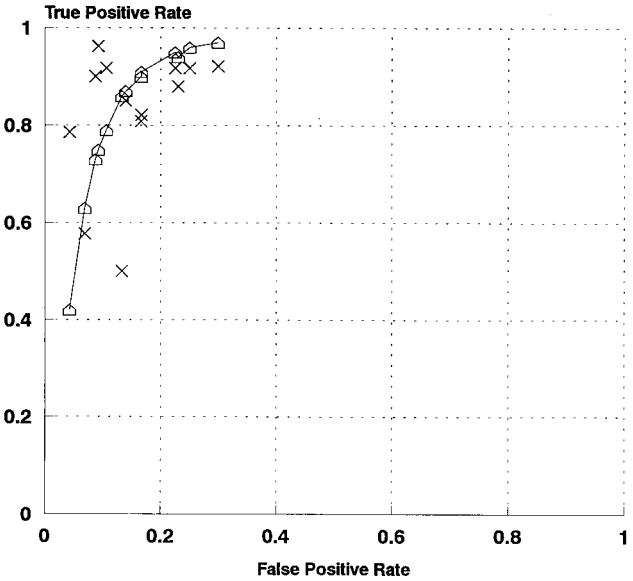

FIG. 1. Graph of summary ROC curve showing true positive rate versus false positive rate for semiquantitative catheter segment culture. The Xs represent actual datum points from individual studies, and the pentagons represent the resulting ROC curve.

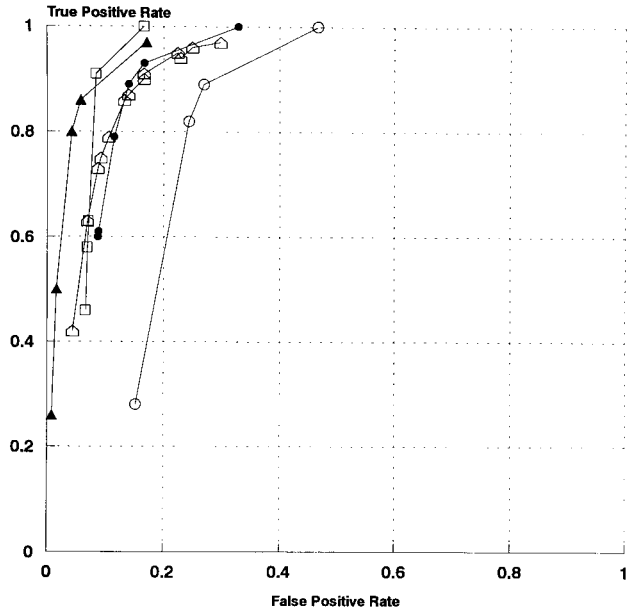

FIG. 2. Graph of summary ROC curves of true positive rates versus false positive rates for five methods for diagnosing catheter-related bloodstream infection: qualitative catheter segment culture (open circle), semiquantitative catheter segment culture (open pentagon), quantitative catheter segment culture (open square), unpaired qualitative blood culture (closed circle), and unpaired quantitative blood culture (closed triangle).

several methods evaluated (83). A majority of the published studies regarding diagnosis of catheter infection could not be included in this review because they did not focus upon bloodstream infection, did not provide primary data, or described a method for which confirmatory data were not yet available from subsequent studies.

The data included in the meta-analysis represented the best studies available in the medical literature regarding six of the more commonly studied tests for diagnosing catheter-related bloodstream infection. Unfortunately, many of these studies included the results of the method being tested in their gold standard definition of catheter-related bloodstream infection, potentially inflating perceived accuracy and compromising the validity of their results (7, 11, 14, 16, 35, 51, 53, 70, 72). We do not believe, however, that the greater perceived accuracy with quantitative catheter segment cultures was due merely to greater levels of incorporation bias, as this bias appeared to be present in a majority of the studies of each of the different catheter segment culture methods. It is likely that the estimated accuracy of each of these methods was somewhat inflated by this bias. Four studies of catheter segment culture methods excluded the culture method being studied from the

TABLE 5. Estimated cost for each microbiologic method

Test method	Estimated cost ($)	
	Per test	Per accurate result
Qualitative catheter segment culture	57.05	467.00
Semiquantitative catheter segment culture	38.63	401.38
Quantitative catheter segment culture	88.71	415.62
Unpaired qualitative catheter blood culture	37.77	271.44
Unpaired quantitative catheter blood culture	60.22	198.18
Paired quantitative catheter blood cultures	120.44	282.17

definition (20, 21, 58, 59), and several of the studies of blood culture methods also attempted to avoid incorporation bias by using a catheter segment culture method to determine that bloodstream infection was due to the catheter as part of their gold standard (8, 13, 27, 62, 89). The disadvantage of this approach, however, was that their gold standard was clearly neither 100% sensitive nor 100% specific. Most of the studies evaluated only one or two tests; the data would have been stronger if several tests were given to each patient in each study. There were only four to six studies available for all but one of the six test methods included in this review; this small number of studies results in limited statistical power to assess the dependence of accuracy on study quality versus patient characteristics and test threshold.

The paired quantitative method appeared to be the most accurate of the blood culture methods evaluated by mean Youden index, but this trend was not confirmed statistically. The ROC curve for this method did not converge appropriately, partly because three studies showed high sensitivity and specificity while one had much lower values. The large unpublished study mentioned above reported very low sensitivity for this method, ranging from 20 to 40% for cultures aspirated through each lumen of short-term triple lumen catheters (83). More studies are needed regarding this issue.

The cost-effectiveness of the various proposed tests depends on the cost of the test, the accuracy of the method, and the excess hospital costs generated by false results. The additional pressure for selection of antibiotic resistance caused by inappropriate therapy for false positive results should be considered a potential cost for less accurate tests, but this cost would be difficult to quantitate. Quantitative culture of blood aspirated from the catheter was the most cost-effective test in the meta-analysis but had only 78% sensitivity. For catheters in place for shorter durations, such quantitative blood cultures have had even lower sensitivity (83). The quantitative catheter segment culture appears from available data to be the most accurate test available at this time and may be the optimal test for epidemiologic studies involving catheters in place less than 2 weeks.

Although the semiquantitative catheter segment culture is one of the least expensive tests for the microbiology laboratory to perform and the most frequently used method in hospital laboratories, it appears to be less accurate than the quantitative methods mentioned above. For long-term tunneled catheters it would clearly cost the hospital as a whole more than a quantitative blood culture drawn from the catheter. For short-term nontunneled catheters, semiquantitative culture may provide slightly lower cost per accurate test result than the quantitative catheter segment culture, as in our analysis. It should be noted, however, that all of the costs of inaccurate test results could not be included in our analysis, and that the difference in costs between these two tests in our analysis represented only 3.5% of the overall cost of evaluating a patient for suspected catheter-related bloodstream infection. This small relative increase in cost may be justified by the 9% increase in sensitivity and the 7% increase in specificity with the quantitative catheter segment culture compared with the semiquantitative method.

In conclusion, quantitative culture demonstrated the greatest accuracy for documenting catheter-related bloodstream infection with culture of a catheter segment by both ROC analysis and Youden index. This was the only method associated with pooled sensitivity and specificity above 90%. The most cost-effective test was a single quantitative blood culture aspirated from the catheter. The sensitivity of quantitative blood cultures from catheters was low, however, especially for short-term catheters.

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