Meta-Analysis: Methods for Diagnosing Intravascular Device–Related Bloodstream Infection

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Background: **No consensus exists on the best methods for diagnosis of intravascular device (IVD)–related bloodstream infection.**

Purpose: **To identify the most accurate methods for diagnosis of IVD-related bloodstream infection.**

Data Sources: **51 English-language studies published from 1966 to 31 July 2004.**

Study Selection: **Studies of diagnostic tests for IVD-related bloodstream infection that described a reference standard and provided sufficient data to calculate sensitivity and specificity.**

Data Extraction: **Study quality, diagnostic tests examined, patient characteristics, prevalence, sensitivity, and specificity.**

Data Synthesis: **Pooled sensitivity and specificity were calculated for 8 diagnostic methods. Summary measures of accuracy were Q* (the upper leftmost point on the summary receiver-operating characteristic curve) and mean *D* (a log odds ratio). Subgroup analyses were used to assess heterogeneity. Overall, the most accurate test was paired quantitative blood culture (Q* = 0.94 [95% CI, 0.88 to 1.0]), followed by IVD-drawn qualitative blood culture (Q* = 0.89 [CI, 0.79 to 0.99]) and the acridine orange leukocyte cytospin test (Q* = 0.89 [CI, 0.79 to 0.91]). The most accurate catheter segment culture test was quantitative culture (Q* = 0.87 [CI, 0.81 to 0.93]), followed by semi-quantitative culture (Q* = 0.84 [CI, 0.80 to 0.88]). Significant heterogeneity in pooled sensitivity and specificity was observed across all test categories.**

Limitations: **The limited number of studies of some of the diagnostic methods precludes precise estimates of accuracy.**

Conclusions: **Paired quantitative blood culture is the most accurate test for diagnosis of IVD-related bloodstream infection. However, most other methods studied showed acceptable sensitivity and specificity (both >0.75) and negative predictive value (>99%). The positive predictive value of all tests increased greatly with high pretest clinical probability. Catheters should not be cultured routinely but rather only if IVD-related bloodstream infection is suspected clinically.**

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Safe and reliable vascular access is essential to modern medical practice. Nearly 200 million intravascular devices (IVDs) are sold in the United States every year (1). Noncuffed percutaneously inserted catheters placed in the femoral, internal jugular, or subclavian vein are the most common centrally placed devices for short-term use, with more than 7 million sold each year (2). Devices for intermediate- and long-term venous access include cuffed and tunneled surgically implanted catheters; totally implantable subcutaneous ports; and, most recently, peripherally inserted central venous catheters (3–7).

The most common life-threatening complication of vascular access is bloodstream infection caused by colonization of the implanted IVD or contamination of the catheter hub or infusate administered through the device (2, 8). Central venous catheters of all types are the most frequent cause of nosocomial bloodstream infection (2, 9–12), and an estimated 250 000 to 500 000 episodes of IVD-related bloodstream infection occur in the United States annually (9–14). These episodes are associated with an attributable mortality rate of 12% to 25% (15, 16), prolongation of hospitalization by 10 to 40 days (15, 17), and marginal cost to the health care system of up to $35 000 per episode (13–18).

Accurate and early diagnosis is essential to guide management of IVD-related bloodstream infection. A variety of diagnostic tests that are based on current understanding of the pathogenesis of IVD-related bloodstream infection (12) have been developed (19–23). They can be broadly categorized as methods that necessitate removal of the IVD and those that do not require removal of the IVD (**Table 1**, Appendix [available at www.annals.org]).

We performed a meta-analysis to determine the most accurate diagnostic methods for IVD-related bloodstream infection.

METHODS

Search and Selection Processes

We searched the MEDLINE database (1966 to 31 July 2004), Current Contents (1993 to 31 July 2004), PubMed (1966 to 31 July 2004), and the Cochrane Network by using the search terms *intravascular device, vascular catheter, bloodstream infection, diagnosis, blood cultures,* and *infection,* and combinations of these terms. Abstracts of meetings of the InterScience Conference on Antimicrobial Agents and Chemotherapy, the American Society of Microbiology, the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Association for Professionals in Infection Control were

See also:

Web-Only
Appendix
Appendix Table
Conversion of tables and figures into slides

Table 1. **Major Diagnostic Methods for Intravascular Device–Related Bloodstream Infection***

Diagnostic Method	Description	Criteria for Positivity
Methods requiring device removal		
Qualitative catheter segment culture (24)	A segment from the removed catheter is immersed in broth media and incubated for 24–72 h	Any growth
Semi-quantitative catheter segment culture (25)	A 5-cm segment of the catheter is rolled 4 times across a blood agar plate and incubated	≥15 CFU
Quantitative catheter segment culture (26–28)	A segment from the removed catheter is flushed with broth (45) or sonicated in broth (65), followed by serial dilutions, surface plating on blood agar, and incubation	≥1000 CFU
Methods not requiring device removal		
Qualitative blood culture through the device (29)	One or more conventional blood cultures are drawn through the device	Any growth
Quantitative blood culture through the device (30, 31)	A blood culture drawn through the device and processed by pour-plate methods or a lysis–centrifugation technique (Isolator, Wampole Laboratories, Cranbury, New Jersey)	≥100 CFU/mL
Paired quantitative blood cultures (32–34)	Concomitant quantitative blood cultures are drawn through the device and percutaneously	Cultures are positive from both sites and the concentration of microorganisms in the culture from the device is 3- to 5-fold greater than in the peripherally drawn culture
Differential time to positivity (35, 36)	Concomitant conventional blood cultures are drawn through the device and percutaneously and are monitored continuously	Both blood cultures are positive and the catheter-drawn blood culture turns positive ≥2 h earlier than the peripherally drawn culture
Acridine orange leukocyte cytospin (37)	Approximately 1 mL of blood is aspirated from the catheter; the cells are lysed with sterile water; and the specimen is centrifuged, stained with acridine orange, and examined microscopically	Visualization of any microorganisms

* CFU = colony-forming units.

also reviewed. References from recent published reviews (1–3, 7, 12, 13, 19–23, 38–43) and a previous meta-analysis (30) were also searched.

Included studies had to evaluate a diagnostic method for IVD-related bloodstream infection compared with a reference standard and provide sufficient data to calculate the sensitivity and specificity of the test. We excluded case reports, review articles, and non–English-language articles. Studies that assessed the utility of blood cultures drawn from venous or arterial catheters to test for true bacteremia as opposed to contamination were also excluded (44, 45), as were studies of IVD colonization rather than IVD-related bloodstream infection.

Data Extraction

We used a standard form to extract data on study quality, diagnostic methods studied, reference standard used, patient characteristics, duration of catheterization, antibiotic use, prevalence, sensitivity, and specificity.

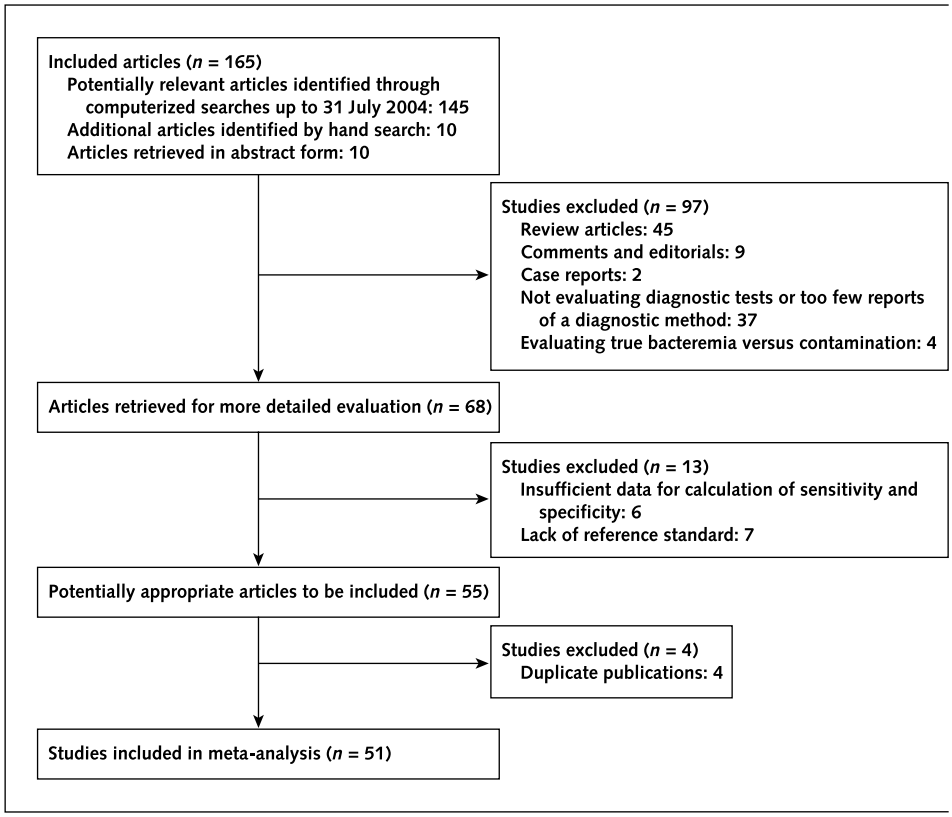
The Standards for Reporting of Diagnostic Accuracy statement and other published criteria were used to assess study quality (46–48). We evaluated studies for description of the sample; setting; type of IVD studied; method of participant recruitment (all patients with IVDs as opposed to only those with suspected IVD-related bloodstream infection); design (retrospective or prospective); reference standard; definition of cut-off values for positivity; whether evaluators of the test were blinded to the results; statistical methods used to compare diagnostic accuracy and precision; description of indeterminate results; subgroup analyses; and presence of biases that may affect study results, such as incorporation bias (in which the test being studied is part of the reference standard) and work-up bias (46).

Data Synthesis

We studied the 8 diagnostic methods that are most frequently used in clinical practice and for which performance data have been published: qualitative catheter segment culture, semi-quantitative catheter segment culture (roll-plate method), or quantitative catheter segment culture, each combined with demonstrated concordance with results of concomitant blood cultures; qualitative blood culture drawn through an IVD; quantitative blood culture drawn through an IVD; paired quantitative peripheral and IVD-drawn blood cultures; acridine orange leukocyte cytospin testing of IVD-drawn blood; and differential time to positivity of concomitant qualitative IVD-drawn and peripheral blood cultures (>2 hours).

We did not include endoluminal brushing in the meta-analysis because few studies have assessed the test. Four of the 5 studies identified (37, 49–52) were performed by the same group of investigators, and 1 study did not define IVD-related bloodstream infection (51). We also excluded studies of cultures of catheter insertion sites

Figure 1. **Literature search leading to the final selection of articles.**



or hubs because of methodologic differences among the studies and a wide range of cut-points for positivity.

Statistical Analysis

We calculated pooled sensitivities and specificities and 95% CIs for each category of diagnostic tests and an estimate of overall sensitivity and specificity by using a random-effects model and estimating equations similar to those proposed by Zhou and colleagues (53). Heterogeneity in the estimates of sensitivity and specificity was assessed by using the Pearson chi-square test or the Fisher exact test.

To combine sensitivity and specificity, we used the approach of Moses and coworkers (54) and calculated D = logit (TPR) − logit (FPR) and S = logit (TPR) + logit (FPR), where *TPR* is the true-positive rate or sensitivity and *FPR* is the false-positive rate (1 − specificity). *D* is interpreted as the log odds ratio, that is, the ratio of the odds that a person who has IVD-related bloodstream infection tests positive to the odds that a person who does not have the disease tests positive for it. We calculated the mean and median values of *D* by using the values computed within each study.

Using the summary receiver-operating characteristic (ROC) curve method of Moses and coworkers (54), we also calculated Q*, which corresponds to the upper leftmost point on the summary ROC curve, where sensitivity equals specificity. The summary measure Q* has been advocated over area under the curve because it is meaningful in the ROC region of greatest interest (54, 55).

The ROC curves were derived from linear regressions of *D* on *S* and account for random thresholds across studies, as discussed by Moses and coworkers (54). Because the tests for homogeneity were significant, the measure Q* may be better suited to comparing tests than are measures that do not adjust for these differences, since it accounts for random thresholds. The regression model was fit by using equally weighted least squares with the function *1m* in S-PLUS software, version 3.4 (MathSoft, Inc., Seattle, Washington), and a robust resistant method using median regression implemented in *11fit* in S-PLUS software (54). The 95% CIs were reported for mean *D* and for Q* based on the equally weighted least-squares method. Differences in mean *D* across all tests were evaluated by using analysis of variance of *D* computed within individual studies.

We also assessed whether increasing degrees of quantitation for methods of catheter segment culture and blood culture would improve the accuracy of the tests. For mean *D*, separate linear regression analyses were performed for each set of tests, with a covariate for level of quantitation that was coded as an ordinal variable. The same analysis was also done for summary ROC curves (54).

Table 2. **Summary Data for Studies Included in the Meta-Analysis**

Study, Year (Reference)	Diagnostic Technique	Duration of Catheterization	Prevalence, %	Test Results, *n*			
				True-Positive	False-Positive	True-Negative	False-Negative
Maki et al., 1977 (64)	Qualitative catheter segment culture	Short term	10	5	21	24	0
Maki et al., 1977 (25)	Qualitative catheter segment culture	Short term	1.6	4	37	209	0
Cleri et al., 1980 (26)	Qualitative catheter segment culture	Short term	9.3	13	33	103	0
Jones et al., 1986 (56)	Qualitative catheter segment culture	Short and long term	3.1	12	99	268	0
Nahass et al., 1990 (57)	Qualitative catheter segment culture	Short term	8.7	5	25	48	2
Whitman and Boatman, 1995 (58)	Qualitative catheter segment culture	Long term	65.5	13	2	8	6
Cooper and Hopkins, 1985 (59)	Semi-quantitative catheter segment culture	Short term	3.6	12	29	289	0
Gutierrez et al., 1992 (60)	Semi-quantitative catheter segment culture	Short term	12.2	10	14	72	2
Cercenado et al.,1990 (61)	Semi-quantitative catheter segment culture	Short term	12.9	17	36	85	1
Rello et al., 1991 (92)	Semi-quantitative catheter segment culture	Short term	13.2	13	18	67	0
Maki et al., 1977 (25)	Semi-quantitative catheter segment culture	Short term	1.6	4	21	225	0
Aufwerber et al., 1991 (63)	Semi-quantitative catheter segment culture	Short term	3.1	15	122	403	2
Kite et al., 1999 (37)	Semi-quantitative catheter segment culture	Short and long term	44.6	45	28	34	5
Kite et al., 1997 (52)	Semi-quantitative catheter segment culture	Short term	9.8	18	69	133	4
Maki et al., 1977 (64)	Semi-quantitative catheter segment culture	Short term	10.0	5	11	34	0
Raad et al., 1992 (65)	Semi-quantitative catheter segment culture	Short term	13.2	8	15	96	9
Snydman et al., 1982 (29)	Semi-quantitative catheter segment culture	NR	6.6	5	7	63	0
Collignon et al., 1986 (66)	Semi-quantitative catheter segment culture	Short term	1.7	11	122	610	2
Widmer et al., 1992 (67)	Semi-quantitative catheter segment culture	Short term	3.8	5	6	145	1
Jones et al., 1986 (56)	Semi-quantitative catheter segment culture	Short and long term	3.1	7	25	342	5
Maki et al., 1996 (68)	Semi-quantitative catheter segment culture	Short term	2.7	10	93	296	1
Collignon et al.,1987 (93)	Semi-quantitative catheter segment culture	Short and long term	3.1	5	41	271	5
Moyer et al., 1983 (70)	Semi-quantitative catheter segment culture	Short term	6.8	5	15	53	0
Widmer et al., 2003 (71)	Semi-quantitative catheter segment culture	Short term	6.8	55	19	913	13
Rello et al., 1989 (92)	Semi-quantitative catheter segment culture	Long term	16.0	6	12	30	2
Widmer et al., 2003 (71)	Quantitative catheter segment culture	Short term	6.8	42	19	913	26
Rello et al., 1989 (92)	Quantitative catheter segment culture	Long term	16.0	5	5	37	3
Cleri et al., 1980 (26)	Quantitative catheter segment culture	Short term	8.7	13	11	125	0
Brun-Buisson et al., 1987 (27)	Quantitative catheter segment culture	Short term	6.0	20	24	287	0
Rello et al., 1991 (62)	Quantitative catheter segment culture	Short term	13.2	7	13	72	6
Kite et al., 1999 (37)	Quantitative catheter segment culture	Short term	44.6	48	15	47	2
Gutierrez et al., 1992 (60)	Quantitative catheter segment culture	Short term	12.2	11	14	72	1
Kite et al., 1997 (52)	Quantitative catheter segment culture	Short term	9.0	15	32	170	5
Sherertz et al., 1990 (28)	Quantitative catheter segment culture	Short term	70.1	68	5	11	13
Raad et al., 1992 (65)	Quantitative catheter segment culture	Short term	15.3	13	5	72	1

Table continued on pp 455, 456, and 457.

A difficulty with mean and median *D* and with Q* based on summary ROC curves is that these measures do not account for the prevalence of the disease in the group of interest (54). In selecting a test for clinical use, its prac-

Table 2—**Continued (*top right*)**

Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Indeterminate Test Results, *n/n*†
100	53	19	100	NR
100	85	9	100	NR
100	76	28	100	NR
100	73	10	100	NR
71	66	17	96	NR
68	80	86	57	NR
100	91	29	100	NR
83	84	41	97	NR
94	70	32	98	0
100	79	41	100	NR
100	91	16	100	NR
88	77	10	99	NR
90	55	62	87	NR
82	66	21	97	NR
100	76	31	100	NR
47	86	35	91	NR
100	90	41	100	NR
85	83	8	99	NR
83	96	45	96	NR
58	93	21	93	NR
91	76	9	99	NR
50	87	10	98	NR
100	78	25	100	NR
81	98	74	99	NR
75	71	33	93	NR
62	98	69	99	NR
63	88	50	92	NR
100	92	54	100	NR
100	92	45	100	0
54	85	35	92	NR
96	76	76	95	NR
92	84	44	98	NR
75	84	32	97	NR
84	69	93	45	NR
93	94	72	99	NR

tical utility will depend not only on its operating characteristics (sensitivity and specificity) but also the patients in which it is being used. The relevant quantities for decision making in this setting are positive predictive value and negative predictive value. We determined positive predictive value and negative predictive value over a wide range of prevalences for each of the tests, on the basis of prevalences from the studies in this meta-analysis. Pooled estimates of sensitivity and specificity were used in these calculations.

Heterogeneity was assessed by using 2 subgroup analyses. One subgroup analysis was done to determine whether duration of IVD implantation affected the diagnostic accuracy of the various tests. Studies that did not report the type of IVD studied or that used a mix of short- and long-term catheterization were excluded from this analysis. For each diagnostic test category, pooled sensitivity, specificity, and mean *D* were calculated separately for short- and long-term catheter placement. The Fisher exact test was used to test the equivalence of sensitivity and specificity for short- and long-term catheterization in each diagnostic test category.

Performance of a diagnostic test may differ depending on the reference standard used for comparison. Several reference standards have been used in studies of diagnostic tests for IVD-related infection. We performed subgroup analysis to compare test performance according to type of reference standard used. We categorized reference standards into those based on catheter segment culture, which include qualitative, semi-quantitative, and quantitative catheter segment cultures, in conjunction with a qualitative blood culture, and those based on IVD-sparing blood culture, which include paired qualitative or quantitative cultures of blood drawn from the IVD and a peripheral site. Studies of diagnostic tests that used other reference standards were excluded from the subgroup analysis. The **Appendix Table** (available at www.annals.org) shows the reference standards used in each study.

For each diagnostic test, we calculated pooled sensitivity, specificity, and mean *D* separately according to reference standard used. The Fisher exact test was used to test the equivalence of sensitivity and specificity.

All statistical analyses were performed by using S-PLUS software (MathSoft, Inc., Seattle, Washington).

Role of the Funding Source

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RESULTS

Fifty-one studies were included in the meta-analysis (25–29, 31–37, 49, 56–93), from an initial review of 185 articles. **Figure 1** shows the literature search leading to selection of the final 51 articles. **Table 2** and the **Appendix Table** (available at www.annals.org) show detailed characteristics of these studies (25–29, 31–37, 49, 52, 56–93).

Table 2—**Continued (*bottom left*)**

Study, Year (Reference)	Diagnostic Technique	Duration of Catheterization	Prevalence, %	Test Results, *n*			
				True-Positive	False-Positive	True-Negative	False-Negative
Maki et al., 1996 (68)	Quantitative catheter segment culture	Short term	2.7	8	66	323	3
Kelly et al., 1996 (73)	Quantitative catheter segment culture	Short term	3.4	13	98	293	1
Douard et al., 1999 (32)	Quantitative catheter septum culture	Long term	8.8	14	0	155	1
Bjornson et al., 1982 (75)	Quantitative catheter segment culture	Short and long term	13.5	8	4	60	2
Snydman et al., 1982 (29)	IVD-drawn qualitative blood culture	NR	0.05	2	8	87	3
Bozzetti et al., 1985 (76)	IVD-drawn qualitative blood culture	Short term	3.1	7	35	213	1
Paya et al., 1989 (77)	IVD-drawn qualitative blood culture	Short term	28.8	15	12	25	0
Whitman and Boatman, 1995 (58)	IVD-drawn qualitative blood culture	Long term	65.5	16	3	7	3
Raucher et al., 1984 (78)	IVD-drawn qualitative blood culture	Long term	6.5	9	21	107	0
Capdevila et al., 1992 (31)	IVD-drawn qualitative blood culture	Short term	15.8	17	10	80	0
Moyer et al., 1983 (70)	IVD-drawn qualitative blood culture	Short term	6.0	4	5	58	0
Paya et al., 1989 (77)	IVD-drawn quantitative blood culture	Short term	28.8	12	6	31	3
Snydman et al., 1982 (29)	IVD-drawn quantitative blood culture	NR	0.05	1	5	90	4
Raucher et al., 1984 (78)	IVD-drawn quantitative blood culture	Long term	6.5	9	5	123	0
Capdevila et al., 1992 (31)	IVD-drawn quantitative blood culture	Short term	15.8	14	1	89	3
Moyer et al., 1983 (70)	IVD-drawn quantitative blood culture	Short term	7.4	4	0	62	1
Franklin et al., 2004 (91)	IVD-drawn quantitative blood culture	Long term	58.0	111	36	65	29
Catton et al., 2002 (94)	IVD-drawn quantitative blood culture	Long term	40.4	80	11	111	3
Flynn et al., 1988 (34)	Paired Lysis–centrifugation‡ quantitative blood cultures	Long term	61.5	7	0	5	0
Sanchez-Conde, 2003 (79)	Paired Lysis–centrifugation‡ quantitative blood cultures	Short term	73.6	106	1	51	39
Douard et al., 1991 (74)	Paired Lysis–centrifugation‡ quantitative blood cultures	Long term	13.2	7	0	46	0
Douard et al., 1994 (33)	Paired Lysis–centrifugation‡ quantitative blood cultures	Short and long term	62.0	30	0	22	6
Mosca et al., 1987 (80)	Paired Lysis–centrifugation‡ quantitative blood cultures	Long term	30.7	8	0	18	0
Paya et al., 1989 (77)	Paired Lysis–centrifugation‡ quantitative blood cultures	Short term	28.8	7	4	33	8
Fortun et al., 2000 (81)	Paired Lysis–centrifugation‡ quantitative blood cultures	Short term	18.6	21	3	93	1
Capdevila et al., 1992 (31)	Paired quantitative blood cultures	Short term	15.8	16	0	90	1
Raucher et al., 1984 (78)	Paired quantitative blood cultures	Long term	19.2	5	0	21	0
Douard et al., 1999 (32)	Paired Lysis–centrifugation‡ quantitative blood cultures	Long term	8.8	12	0	155	3
Blot et al., 1999 (35)	Differential time to positivity	Short and long term	19.7	16	1	68	1
Malgrange et al., 2001 (83)	Differential time to positivity	Long term	35.7	27	29	34	8
Sanchez-Conde, 2003 (79)	Differential time to positivity	Short term	73.6	135	5	47	10
Rjinders et al., 2001 (84)	Differential time to positivity	Short term	30.0	2	4	3	1
Blot et al., 1998 (82)	Differential time to positivity	Long term	66.6	27	0	14	1
Gaur et al., 2002 (89)	Differential time to positivity	Long term	28.5	8	0	24	1
Mermel et al., 1998 (85)	Differential time to positivity	NR	46.8	11	5	12	4
Raad et al., 2004 (90)	Differential time to positivity	Short term*	48.0	29	3	36	7
Raad et al., 2004 (90)	Differential time to positivity	Long term	62.0	67	11	33	5
Seifert et al., 2003 (36)	Differential time to positivity	Short term	43.1	18	4	25	4
Rushforth et al., 1993 (86)	Acridine orange leukocyte cytospin	Long term	32.6	27	4	60	4
Tighe et al., 1996 (49)	Acridine orange leukocyte cytospin	NR	14.0	2	0	43	5
Baum et al., 1998 (87)	Acridine orange leukocyte cytospin	Short term	28.5	2	2	8	2
Kite et al., 1999 (37)	Acridine orange leukocyte cytospin and Gram stain	Short and long term	44.6	48	5	57	2
Bong et al., 2003 (88)	Acridine orange leukocyte cytospin	Short term	20.0	10	4	36	0

* IVD = intravascular device; NR = not reported.
† Indeterminate test results were not included in calculation of the test performance.
‡ Isolator system (Wampole Laboratories, Cranbury, New Jersey).

Although a majority of the studies provided information on the composition of the sample (57%) and eligibility criteria (92%), incorporation bias was present in 51% of studies, 4 studies (8%) reported subgroup analyses, and 8% provided numerical precision for test indices (SEs or CIs). Only 1 study reported cost data (88), and only 1 reported effects on patient outcome (67).

Table 3 shows the pooled and overall sensitivity and

Table 2—**Continued (*bottom right*)**

Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Indeterminate Test Results, *n/n*†
73	83	11	83	NR
93	75	11	99	NR
93	100	100	99	NR
80	94	100	98	NR
40	92	20	96	NR
88	86	16	99	NR
100	68	55	100	NR
84	70	84	70	NR
100	84	30	10	NR
100	89	62	100	NR
100	92	44	100	NR
80	84	66	91	NR
20	95	16	95	NR
100	96	64	100	NR
82	99	93	96	NR
80	100	100	98	NR
79	64	79	69	NR
96	91	88	97	NR
100	100	100	100	1/13
73	98	99	56	NR
100	100	100	100	NR
83	100	100	78	NR
100	100	100	100	NR
47	89	63	80	NR
95	97	87	98	NR
94	100	100	98	NR
100	100	100	100	NR
80	100	100	98	NR
94	99	94	91	19/93
77	54	48	54	0
93	90	96	82	NR
67	43	33	75	25/37
96	100	100	93	22/64
89	100	100	96	24/57
73	71	68	75	0
81	92	91	84	5947/6138
93	75	86	87	5947/6138
82	86	81	86	NR
87	94	87	93	NR
29	100	100	89	NR
50	80	50	80	NR
96	92	90	96	0
100	90	71	100	NR

specificity for each diagnostic method. Heterogeneity was present in the estimates of sensitivity and specificity, except for the specificity of the acridine orange leukocyte cytospin test ($P = 0.12$). Overall sensitivity for a single test method was highest for qualitative catheter segment culture (0.90), followed by IVD-drawn qualitative blood culture (0.87) and paired quantitative blood cultures (0.87). The acridine orange leukocyte cytospin test had the lowest overall sensitivity (0.72). Paired quantitative blood cultures (0.98) had the highest specificity, followed by the acridine orange leukocyte cytospin test (0.91) and IVD-drawn quantitative blood culture (0.90), whereas qualitative catheter segment culture had the lowest specificity (0.72).

The results of the pooled estimates and overall (random-effects) estimates of sensitivity and specificity were similar for each diagnostic method. The biggest differences were in the sensitivities for differential time to positivity, paired quantitative blood cultures, and acridine orange leukocyte cytospin test, which were influenced by smaller studies whose sensitivities differed somewhat from those in larger studies. These smaller studies tend to be weighted more heavily in the random-effect estimates.

Our analysis shows that the most accurate diagnostic test was paired quantitative blood cultures (mean *D*, 5.73 [95% CI, 4.68 to 6.77]), followed by IVD-drawn quantitative blood culture (mean *D*, 4.20 [CI, 2.72 to 5.67]) and semi-quantitative catheter segment culture (mean *D*, 3.97 [CI, 3.04 to 4.89]) (**Table 3**). With Q* used as the measure of diagnostic accuracy, the ranking of the 2 most accurate tests did not change. The rankings of the other tests are similar but not identical across the measures. The largest difference in ranking for a test across 2 measures is 2; therefore, the rank of individual tests did not change materially between the 2 analyses. Differences in mean *D* across all test categories were statistically significant ($P = 0.027$). Because the tests of heterogeneity were significant, Q* may be better suited to comparing tests than are measures that do not account for heterogeneity.

Diagnostic Methods Requiring Removal of the Device

Qualitative Culture of Catheter Segment

In the 6 studies analyzed (**Appendix Table**), qualitative culture of the catheter segment was found to have poor specificity (0.72 [CI, 0.66 to 0.78]) but high sensitivity (0.90 [CI, 0.83 to 0.97]). It was the least accurate of the tests studied.

Semi-quantitative Catheter Segment Culture

Nineteen studies (of which 18 were prospective and 1 retrospective) of semi-quantitative catheter segment culture qualified for our analysis (**Table 2**, **Appendix Table**). Fourteen studies included short-term catheterization, 1 included only long-term catheterization, and 3 included both short- and long-term catheterization. Four studies included only patients in whom IVD-related bloodstream infection was suspected, and 15 studies used all catheter segments sent to a laboratory at IVD removal.

The overall sensitivity across 19 studies was 0.85 (CI, 0.81 to 0.89), and specificity was 0.82 (CI, 0.80 to 0.84). Mean *D* was 3.38 (CI, 2.84 to 3.91), and the equally weighted least-squares Q* was 0.84 (CI, 0.80 to 0.88),

Table 3. **Summary Statistics for Diagnostic Tests for Intravascular Device–Related Bloodstream Infection†**

Diagnostic Test	Studies, *n*	Pooled Sensitivity (95% CI)	*P* Value‡	Overall Sensitivity, by Random-Effects Model (95% CI)	Pooled Specificity (95% CI)
Qualitative catheter segment culture	6	0.87 (0.79–0.96)	0.03	0.90 (0.83–0.97)	0.75 (0.72–0.78)
Semi-quantitative catheter segment culture	19	0.83 (0.79–0.87)	0.014	0.85 (0.81–0.89)	0.86 (0.85–0.87)
Quantitative catheter segment culture	14	0.82 (0.78–0.86)	<0.001	0.83 (0.78–0.88)	0.89 (0.87–0.91)
IVD-drawn qualitative blood culture	7	0.91 (0.84–0.98)	0.039	0.87 (0.80–0.94)	0.86 (0.83–0.89)
IVD-drawn quantitative blood culture	7	0.84 (0.80–0.89)	<0.001	0.77 (0.69–0.85)	0.90 (0.88–0.92)
Paired quantitative blood cultures	10	0.79 (0.74–0.84)	0.008	0.87 (0.83–0.91)	0.99 (0.98–1.0)
Acridine orange leukocyte cytospin	5	0.87 (0.80–0.94)	<0.001	0.72 (0.60–0.84)	0.93 (0.89–0.97)
Differential time to positivity	8	0.89 (0.86–0.92)	0.022	0.85 (0.78–0.92)	0.83 (0.79–0.87)

† IVD = intravascular device.
‡ Test for homogeneity.
§ The mean *D* value increases with increasing diagnostic test accuracy.
‖ The value of Q* increases with increasing diagnostic test accuracy.

indicating moderate accuracy. The positive predictive value was low in the setting of low prevalence of IVD-related bloodstream infection; however, it improved to 0.80 at a prevalence (pretest probability) of 0.40 (**Table 4**).

Quantitative Catheter Segment Culture

Fourteen studies of quantitative catheter segment culture met criteria for inclusion in our analysis (**Table 2**, **Appendix Table**). The test had an overall sensitivity of 0.83 (CI, 0.78 to 0.88) and specificity of 0.87 (CI, 0.85 to 0.89). The mean *D* value was 3.97 (CI, 3.04 to 4.89), and the equally weighted least-squares Q* value was 0.87 (CI, 0.81 to 0.93), making it the third most accurate test.

IVD-Sparing Diagnostic Methods

Paired Quantitative Blood Cultures

Ten studies of paired quantitative blood cultures were analyzed, of which 8 used a lysis–centrifugation system (Isolator, Wampole Laboratories, Cranbury, New Jersey) and 2 used pour-plate blood cultures. Most of the devices studied were long-term IVDs, including totally implantable ports. Only 2 studies reported that antibiotics were administered before blood for culture was obtained. Sensitivity was 0.87 (CI, 0.83 to 0.91), and specificity was 0.98 (CI, 0.97 to 0.99). The mean *D* value was 5.73 (CI, 4.68 to 6.77), and Q* was 0.94 (CI, 0.88 to 1.0), suggesting that this test was the most accurate of the techniques studied.

IVD-Drawn Quantitative Blood Culture

Seven studies examined quantitative blood culture drawn through the IVD (**Table 2**, **Appendix Table**), yielding an overall sensitivity of 0.77 (CI, 0.69 to 0.85) and a specificity of 0.90 (CI, 0.88 to 0.92). The mean *D* value was 4.20 (CI, 2.72 to 5.67), and the equally weighed least-squares Q* value was 0.89 (CI, 0.79 to 0.89), making this the second most accurate test.

Table 4. **Performance of Diagnostic Tests, by Prevalence of Intravascular Device–Related Bloodstream Infection***

Diagnostic Test	Studies, *n*	Positive Predictive Value, by Prevalence					Negative Predictive Value, by Prevalence				
		0.01	0.05	0.09	0.2	0.4	0.01	0.05	0.09	0.2	0.4
Qualitative catheter segment culture	6	0.03	0.16	0.26	0.47	0.70	>0.99	0.99	0.98	0.96	0.89
Semi-quantitative catheter segment culture	19	0.06	0.24	0.37	0.60	0.80	>0.99	0.99	0.98	0.95	0.88
Quantitative catheter segment culture	14	0.07	0.28	0.42	0.65	0.83	>0.99	0.99	0.98	0.95	0.88
IVD-drawn qualitative blood culture	7	0.06	0.25	0.39	0.62	0.81	>0.99	0.99	0.99	0.97	0.93
IVD-drawn quantitative blood cultures	7	0.08	0.31	0.45	0.68	0.85	>0.99	0.99	0.98	0.96	0.89
Paired quantitative blood culture	10	0.44	0.81	0.89	0.95	0.98	>0.99	0.99	0.98	0.95	0.88
Acridine orange leukocyte cytospin	5	0.05	0.22	0.34	0.57	0.78	>0.99	0.99	0.99	0.97	0.93
Differential time to positivity	8	0.05	0.21	0.34	0.56	0.77	>0.99	0.99	0.98	0.96	0.91

* IVD = intravascular device.

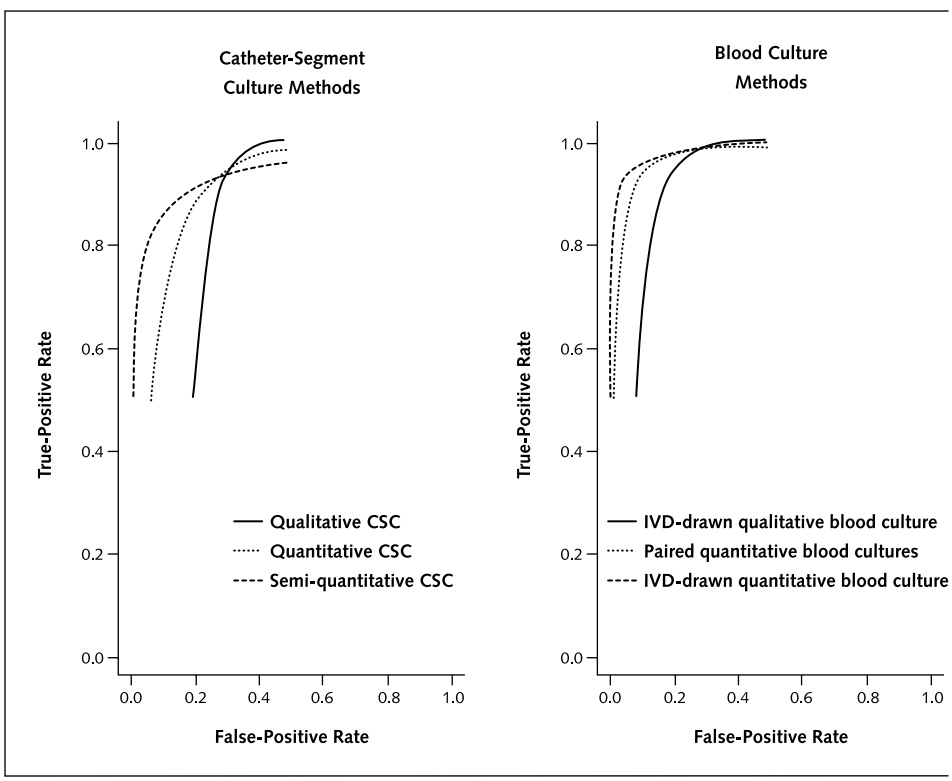
Table 3—**Continued**

P Value‡	Overall Specificity, by Random-Effects Model (95% CI)	Summary Measures of Accuracy		Equally Weighted Least-Squares Q*‖	Robust Q*
		Mean *D* Value§	Median *D* Value		
<0.001	0.72 (0.66–0.78)	3.07 (2.03–4.11)	3.22	0.76 (0.64–0.88)	0.76
<0.001	0.82 (0.80–0.84)	3.38 (2.84–3.91)	3.13	0.84 (0.80–0.88)	0.83
<0.001	0.87 (0.85–0.89)	3.97 (3.04–4.89)	3.73	0.87 (0.81–0.93)	0.86
0.011	0.83 (0.78–0.88)	3.80 (2.81–4.78)	4.14	0.86 (0.80–0.92)	0.85
<0.001	0.90 (0.88–0.92)	4.20 (2.72–5.67)	5.41	0.89 (0.79–0.99)	0.94
0.045	0.98 (0.97–0.99)	5.73 (4.68–6.77)	6.05	0.94 (0.88–1.0)	0.95
0.12	0.91 (0.86–0.96)	3.95 (2.46–5.43)	4.40	0.89 (0.79–0.91)	0.92
<0.001	0.81 (0.75–0.87)	3.66 (2.33–4.98)	3.64	0.85 (0.81–0.97)	0.80

Acridine Orange Leukocyte Cytospin Test

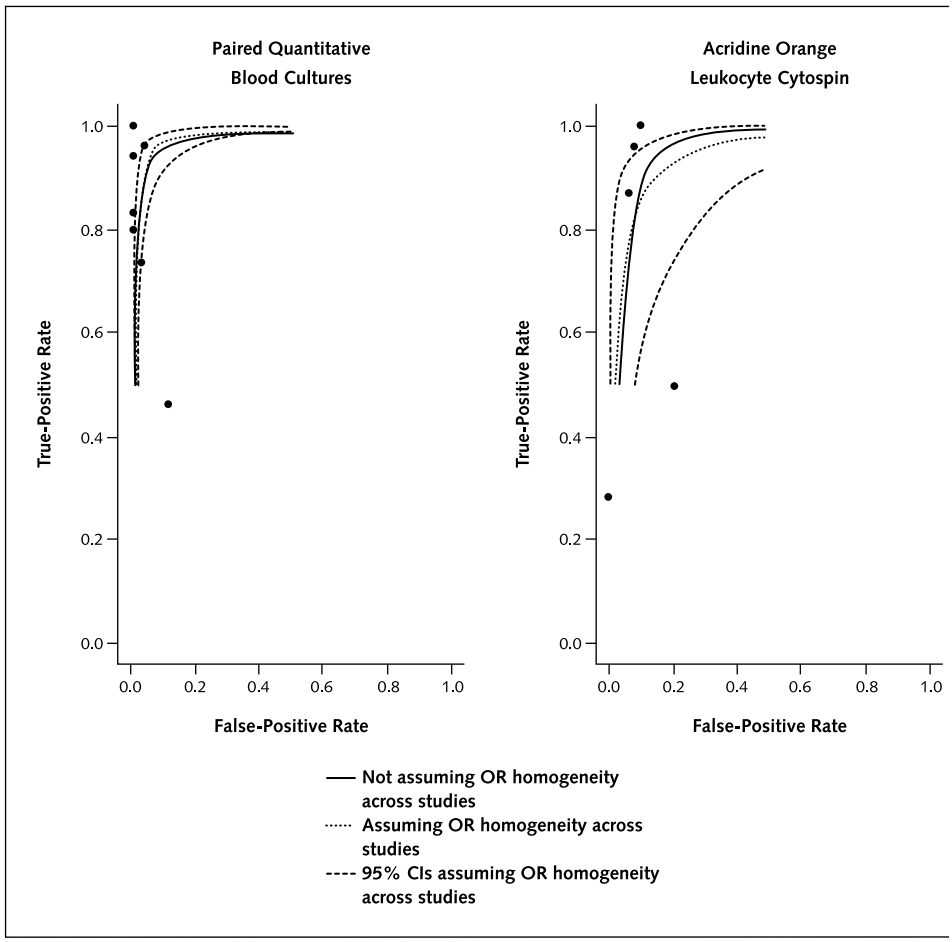
Five studies, all of which were prospective, met our inclusion criteria. Two studied only short-term catheters, 1 studied only long-term catheters, 1 included both types of devices, and 1 did not report the type of devices studied. In all studies, the test was applied only to patients with clin-

Figure 2. **Summary receiver-operating characteristic curves for diagnostic techniques based on catheter segment culture (*CSC*) (*left*) or blood culture (*right*).**



The accuracy of tests based on either type of culture increases as the level of quantitation increases but was statistically significant only for blood culture methods ($P = 0.02$). IVD = intravasucular device.

Figure 3. **Summary receiver-operating characteristic curves for paired quantitative blood culture (*left*) and the acridine orange leukocyte cytospin (*right*).**



Each dot represents 1 study. OR = odds ratio.

ically suspected IVD-related bloodstream infection and the reference standard varied from paired quantitative blood cultures to diverse catheter culture techniques in conjunction with positive peripheral blood cultures.

The overall sensitivity and specificity of the acridine orange leukocyte cytospin test were 0.72 (CI, 0.60 to 0.84) and 0.91 (CI, 0.86 to 0.96), respectively. The mean *D* value of 3.95 (CI, 2.46 to 5.43) and the Q* value of 0.89 (CI, 0.79 to 0.91) indicate that this test was the fourth most accurate test.

IVD-Drawn Qualitative Blood Culture

Seven studies of qualitative blood cultures drawn through the IVD (**Table 2**, **Appendix Table**) were analyzed, yielding an overall sensitivity of 0.87 (CI, 0.80 to 0.94) and a specificity of 0.83 (CI, 0.78 to 0.88). The mean *D* was 3.80 (CI, 2.81 to 4.78) and equally weighted least-squares Q* was 0.86 (CI, 0.80 to 0.92), making this the fifth most accurate test.

Differential Time to Positivity

We analyzed 10 studies that assessed the utility of differential time to positivity for diagnosis of IVD-related bloodstream infection (**Table 2**, **Appendix Table**), of which 8 were prospective and 2 were retrospective. One study evaluated the performance of this diagnostic method in general inpatients, 7 were limited to patients with cancer, and 2 were limited to medical and surgical patients in the intensive care unit who had short-term implantation of devices. In general, differential time to positivity performed well for long-term IVDs, with an overall sensitivity of 0.85 (CI, 0.78 to 0.92) and specificity of 0.81 (CI, 0.75 to 0.87). The mean *D* value was 3.66 (CI, 2.33 to 4.98), and the equally weighted least-squares Q* value was 0.85 (CI, 0.81 to 0.97). Raad and associates (89) recently assessed the utility of the test in a large study. The sensitivity and specificity of differential time to positivity in patients with short-term catheters (<30 days) were 0.81 and 0.92, respectively; for those with long-term catheters (≥30 days), differential time to positivity had a sensitivity of 0.93 and a specificity of 0.75.

Summary ROC Analyses

Linear regression analysis of *D* values and the summary ROC suggested greater accuracy of catheter segment cultures with increasing quantitation, but these findings were not statistically significant. For tests of blood cultures, a statistically significant systematic trend was observed, in that *D* values and summary ROC increased as the level of quantitation increased ($P = 0.02$ for mean *D*).

Figures 2 and **3** show summary ROC curves for catheter segment cultures and blood cultures. The ROC curves for quantitative catheter segment cultures lie closer to the upper left corner of the ROC plot, indicating greater accuracy of this method. Among the blood culture tests, that with the greatest area under the ROC curve is paired quantitative blood culture.

Influence of Pretest Probability on Test Performance

We determined the positive and negative predictive values for all diagnostic methods over a wide range of prevalences of IVD-related bloodstream infection that are likely to be encountered in the clinical setting. Small differences were noted in negative predictive values, whereas the positive predictive value of all tests increased greatly with increasing prevalence (**Table 4**). The ordering of the accuracy of the diagnostic tests (as shown by Q*), however, did not change with increasing prevalence.

Subgroup Analyses

Table 5 shows results of subgroup analysis to compare test accuracy on the basis of duration of catheterization (short or long term). No diagnostic method was found to be systematically superior for duration of catheterization in terms of sensitivity, specificity, or mean *D*. However, the small number of studies available for this analysis precludes drawing firm conclusions.

Subgroup analysis was done to evaluate differences among diagnostic tests according to the reference standard used. For some tests, performance (as measured by mean *D*) differed significantly by choice of reference standard (**Table 6**). However, absolute differences in mean *D* were not substantial, and the hierarchical ranking of the 8 test categories was not materially affected. Few studies of each method used a reference standard based on catheter segment culture or blood culture; these results should therefore be regarded as exploratory.

DISCUSSION

The spectrum of infections caused by IVDs ranges from local colonization (asymptomatic infection) to bacteremia or candidemia with septic shock (2). Clinical findings are unreliable for diagnosing IVD-related bloodstream

Table 5. **Summary Statistics for Diagnostic Tests for Intravascular Device–Related Bloodstream Infection, by Duration of Catheterization**

Diagnostic Test and Duration of Catheterization	Studies, *n*	Pooled Sensitivity	*P* Value	Pooled Specificity	*P* Value	Mean *D* Value
Qualitative catheter segment culture						
Short term	4	0.94		0.76		3.50
Long term	1	0.68	0.016	0.80	>0.2	1.95
Semi-quantitative catheter segment culture						
Short term	14	0.84		0.85		3.63
Long term	1	0.75	>0.2	0.71	<0.001	1.85
Quantitative catheter segment culture						
Short term	11	0.82		0.89		3.76
Long term	2	0.83	>0.2	0.97	<0.001	5.19
IVD-drawn qualitative catheter blood culture						
Short term	4	0.98		0.86		4.42
Long term	2	1.00	>0.2	0.83	>0.2	3.43
IVD-drawn quantitative catheter blood culture						
Short term	3	0.81		0.96		4.76
Long term	1	0.86	>0.2	0.85	<0.001	4.46
Paired quantitative blood cultures						
Short term	4	0.75		0.97		4.98
Long term	5	0.93	0.008	1.00	0.008	6.41
Acridine orange leukocyte cytospin						
Short term	2	0.87		0.88		3.18
Long term	1	0.87	>0.2	0.94	>0.2	4.41
Differential time to positivity						
Short term	4	0.89		0.87		2.96
Long term	4	0.90	>0.2	0.72	0.003	4.20

* IVD = intravascular device.

Table 6. **Summary Statistics for Diagnostic Tests for Intravascular Device–Related Bloodstream Infection, by Reference Standard Used**

Diagnostic Test and Reference Standard Used	Studies, *n*	Pooled Sensitivity	*P* Value	Pooled Specificity	*P* Value	Mean *D* Value
Qualitative catheter segment culture						
Catheter segment culture	4	0.81		0.79		2.98
Blood culture	2	1.00	0.09	0.71	0.005	3.30
Semi-quantitative catheter segment culture						
Catheter segment culture	15	0.84		0.86		3.45
Blood culture	4	0.76	0.2	0.85	>0.2	3.12
Quantitative catheter segment culture						
Catheter segment culture	11	0.83		0.91		4.22
Blood culture	3	0.74	0.19	0.85	<0.001	3.02
IVD-drawn qualitative catheter blood culture						
Catheter segment culture	6	0.90		0.87		3.66
Blood culture	1	1.00	>0.2	0.84	>0.2	4.55
IVD-drawn quantitative catheter blood culture						
Catheter segment culture	5	0.89		0.94		4.28
Blood culture	2	0.81	0.07	0.82	<0.001	3.99
Paired quantitative blood cultures						
Catheter segment culture	6	0.77		0.98		5.64
Blood culture	3	1.00	0.03	1.00	>0.2	6.09
Acridine orange leukocyte cytospin						
Catheter segment culture	4	0.91		0.81		4.04
Blood culture	1	0.88	>0.2	0.87	>0.2	4.14
Differential time to positivity						
Catheter segment culture	5	0.91		0.81		3.76
Blood culture	4	0.88	>0.2	0.87	0.18	4.02

* IVD = intravascular device.

infection because they have poor specificity and sensitivity (95–98). The most common clinical findings have poor specificity (for example, fever with or without chills), and inflammation or purulence around the intravascular device has high specificity but poor sensitivity (95). Which tests are best for diagnosing IVD-related bloodstream infection has been unclear, even though numerous studies have attempted to clarify the matter. This uncertainty is reflected in many of the summary recommendations of a recent Centers for Disease Control Hospital Infection Control Practice Advisory Committee evidence-based guideline (7).

The key findings of our analysis are that with short-term IVDs, quantitative or semi-quantitative culture of the catheter combined with 2 blood cultures (1 drawn percutaneously from a peripheral vein and 1 through the suspect catheter) will allow accurate diagnosis of IVD-related bloodstream infection. Qualitative cultures of catheter segments should no longer be used because this method has poor specificity. With long-term IVDs, paired quantitative blood culture is the most accurate diagnostic method; however, paired (qualitative) conventional blood culture using differential time to positivity provides comparable sensitivity and acceptable specificity, at no increased cost. The acridine orange leukocyte cytospin test offers rapid diagnosis of IVD-related bloodstream infection with similar accuracy but lower sensitivity. When paired blood cultures are used to diagnose IVD-related bloodstream infection, it is essential that the blood cultures are drawn concomitantly (<10 minutes apart), similar volumes of blood are cultured, and blood is obtained before empirical anti-infective therapy begins.

In many centers, central venous catheter tips are routinely cultured on removal. Positive catheter-tip cultures prompt empirical antimicrobial therapy, even in the absence of positive blood cultures or clinical signs of systemic infection. Numerous studies have shown that 15% to 25% of cultures of short-term central venous catheters are colonized, usually by coagulase-negative staphylococci, but most patients have no evidence of infection (99, 100). The practice of giving anti-infective agents to patients with positive catheter-tip cultures with no signs of infection or documented bloodstream infection drives much unnecessary use of vancomycin and other broad-spectrum antibiotics (101), ramping antibiotic pressure that is responsible for the emergence of antimicrobial resistance in hospitals (102).

The Centers for Disease Control Hospital Infection Control Policy Advisory Committee strongly recommends that central venous catheters and other vascular catheters not be cultured unless local inflammation is present at the insertion site or the patient has clinical signs suggestive of bacteremia or candidemia (7, 20). Our analysis (**Table 3**)

shows that if tests for diagnosis of IVD-related bloodstream infection are performed only in patients in whom the pretest clinical probability of bacteremia or candidemia (prevalence > 0.20 to 0.40) is reasonably high, the positive predictive value of a positive test result is much higher ($P < 0.001$) and unnecessary use of anti-infective therapy can be greatly reduced.

Our analysis has limitations stemming from the heterogeneity in the design of the studies analyzed. Although definitions of IVD-related bloodstream infection and reference standards used differed substantially, all studies that we included used acceptable published methods. Several of the diagnostic techniques, particularly those based on IVD-drawn blood culture, would be expected to perform less well if antimicrobial agents were administered before diagnostic testing for IVD-related bloodstream infection; however, few studies reported this information. Disparity also existed in the patients undergoing the test of interest: In most studies, the test was done in patients suspected of having IVD-related bloodstream infection (a high-prevalence group), whereas in others, all catheters were examined at removal (a low-prevalence group). Most studies reviewed also did not report whether they were blinded. Even though significant statistical heterogeneity was observed in most of the pooled test variables, our subgroup analyses to explore the implications of this heterogeneity found no evidence that it materially affected the relative sensitivity, specificity, or accuracy of the test categories (**Tables 3** to **5**).

Finally, no study that we reviewed included catheters coated with anti-infective agents. As use of such catheters becomes more prevalent, the existing definitions of catheter colonization and catheter-related infection may need to be modified because anti-infective coatings may lead to false-negative results on culture (103, 104). Given the importance of IVD-related bloodstream infection as a threat to patient safety, larger and better-designed trials are needed to more reliably characterize the accuracy of the various diagnostic methods for IVD-related bloodstream infection, particularly IVD-sparing techniques.

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Appendix

Methods Requiring Device Removal

Qualitative Culture of Catheter Segment

The qualitative culture technique described by Druskin and Siegel in 1963 (24) involves immersion of the aseptically transected catheter tip in liquid media. Any growth after overnight incubation is considered clinically significant.

Semi-quantitative Catheter Segment Culture (Roll-Plate Method)

The most widely used technique for diagnosing central venous catheter–related bloodstream infection is the semi-quantitative method described by Maki and colleagues (25). A 5-cm catheter segment (or the entire catheter, for short peripheral catheters) is transferred to the surface of a blood agar plate and rolled back and forth across the surface at least 4 times. The plate is examined after overnight incubation, and the presence of 15 or more colony-forming units is considered indicative of catheter colonization (synonymous with local infection of the catheter), the precursor to IVD-related bloodstream infection.

Quantitative Catheter Segment Culture

Although the roll-plate method is very useful, it may be limited in that it samples only the external surface of catheter and may miss organisms that are colonizing the intraluminal surface. This limitation is especially apparent with long-term IVDs, in which the lumen is the predominant site of colonization and cause of bloodstream infection (38). Quantitative culture techniques, in which the catheter segments are flushed or immersed in liquid media and centrifuged or sonicated (28) have been described.

Cleri and coworkers (26) reported a quantitative method of catheter segment culture. The catheter is removed and the intradermal and intravascular segments are excised, immersed in 2 to 10 mL of trypticase–soy broth, and flushed 3 times. The broth is serially diluted 100-fold, and 0.1 mL of each dilution is plated; a cut-off value of 1000 or more colony-forming units is considered positive.

Brun-Buisson and associates (27) modified the technique of Cleri and coworkers. The catheter segment is placed in a dry sterile tube, and 1 mL of sterile water is dripped onto the catheter. After the tube is sonicated for 1 minute, 0.1 mL of fluid is streaked onto a blood agar plate. A colony count of 1000 or more colony-forming units is considered a positive result. Sherertz and associates reported another modification of Cleri and coworkers' technique, in which catheter segments immersed in 1 mL of broth and sonicated for 1 minute, and subcultures of serial dilutions are performed (28).

Direct Staining of the Catheter Segment

A variety of microbial stains applied to removed catheter segments have been studied to facilitate rapid diagnosis of IVD-related bloodstream infection, including Gram stain of the catheter (59) or of the sonication broth (73), or Gram stain or acridine orange stain of an impression smear of the catheter (69, 105). In 1 study, Gram stain of the removed catheter was helpful in the diagnosis of local infections but was substantially less sensitive than semi-quantitative or quantitative culture methods for diagnosis of IVD-related bloodstream infection (59). The technical difficulty of staining and examining a distorted catheter segment, and the prolonged time (>30 minutes) required to examine the stained segments under a light microscope, have limited acceptance of this technique. Because of the heterogeneous methods used and the limited number of studies available, we did not perform statistical analyses for these methods.

IVD-Sparing Diagnostic Methods

It is important to conclusively implicate the IVD before removing a needed device, especially a long-term IVD. Prospective studies have shown that only 25% to 45% of episodes of fever or sepsis in patients with a central venous catheter represent true IVD-related bloodstream infection (99, 100). Development of in situ methods to reliably detect IVD-related bloodstream infection that do not require removal of the IVD would be of great value to clinicians and patients.

IVD-Drawn Qualitative Blood Culture

Because of the difficulty in distinguishing between intraluminal colonization alone and true IVD-related bloodstream infection, the utility of IVD-drawn qualitative blood culture in the absence of a concomitant peripheral blood culture may be limited (44, 45, 106).

IVD-Drawn Quantitative Blood Culture

Evidence indicates that a single quantitative blood culture drawn from a long-term device, even without an accompanying positive culture drawn from the periphery, can accurately identify IVD-related bloodstream infection if more than 100 colony-forming units/mL are found (30, 31).

Paired Quantitative Blood Cultures

Quantitative blood cultures drawn through the IVD and concomitantly by venipuncture from a peripheral vein or another IVD can be used to diagnose IVD-related bacteremia or fungemia without removal of the IVD if empirical antimicrobial therapy has not yet been initiated. Access to a laboratory that can do pour-plate blood cultures or that has an automated quantitative system for culturing blood, such as the lysis–centrifugation system (Isolator [Wampole Laboratories, Cranbury, New Jersey]), is essential. If the IVD is infected, the blood drawn through it usually shows a greater than 5-fold increase in the concentration of organisms compared with the blood drawn percutaneously from a peripheral vein or another IVD. High-grade peripheral candidemia (≥25 colony-forming units/mL) has been reported to indicate an infected IVD 90% of the time (107).

Paired quantitative blood cultures are most useful for diagnosis of infection associated with long-term IVDs. Their utility for diagnosis of infections associated with short-term IVDs has been limited by their expense. Moreover, studies to evaluate the diagnostic utility of this method have used differing cutpoints for paired quantitative blood cultures, ranging from a 3-fold (33),

4-fold (32), or 5-fold (34) difference among concentrations of organisms drawn from the IVD and a peripheral site. Thus, comparison of these studies is difficult.

Differential Time to Positivity

Quantitative blood cultures are labor intensive and expensive. The ubiquity of automated radiometric blood culture systems (BACTEC system [Becton Dickinson, Sparks, Maryland]), in which blood cultures are continuously monitored for microbial growth, has led to a clever application of this system to detect IVD-related bloodstream infection (35): the differential time to positivity of blood cultures drawn through the IVD and concomitantly from a peripheral vein. Positivity in a blood culture drawn from the IVD more than 2 hours before positivity of the culture drawn from a peripheral vein has been reported to be highly predictive of IVD-related bloodstream infection (35, 36).

Acridine Orange Leukocyte Cytospin Test

A simple and rapid method of detecting IVD-related bloodstream infection is the acridine orange leukocyte cytospin test (40). Approximately 1 mL of blood is aspirated from the catheter; the cells are lysed with sterile water; and the specimen is centrifuged, stained with acridine orange, and examined microscopically. The presence of microorganisms constitutes a positive result.

Limited studies have evaluated other stains of IVD-drawn blood, such as Gram stain alone (108, 109), quinacrine (109), or nitroblue tetrazolium (86), but further studies are needed before meaningful conclusions can be drawn about the utility of these stains.

Endoluminal Brushing

In situ testing using a novel culture brush that can be passed down the lumen and out the end of a long-term IVD to pick up luminal biofilm and colonized fibrin and thrombus around the tip has been proposed as an alternative to removal and culture of the IVD (51). The few studies of this technique have yielded discordant results, and iatrogenic procedure-associated bacteremias have been reported with the use of the culture brush (51). Future studies of this method must rigorously assess for adverse effects.

Quantitative Cultures of Catheter Insertion Sites or Catheter Hubs

Quantitative cultures of insertion sites or catheter hubs have been proposed as a simple means of detecting infection of short-term central venous catheters. Most studies have found a fairly high sensitivity but poor specificity (81, 110–114). Therefore, culture of the device insertion site or the hub may be of value to rule out infection of a short-term IVD if the result is negative, but it does not reliably predict infection of the device if the result is positive.

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Appendix Table. **Features of the Included Studies***

Study, Year (Reference)	Diagnostic Test Studied	Criteria for Positivity	Reference Standard Used	Basis of Reference Standard	Study Design	Patients/ Catheters or Infectious Episodes, *n/n*	Sample	Rationale for Performance of Diagnostic Test
Maki et al., 1977 (25)	Qualitative CSC	Any growth	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	250/250	General inpatients	All catheters at removal
Maki et al., 1977 (64)	Qualitative CSC	Any growth	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	6/50	Patients with burns	All catheters at removal
Cleri et al., 1980 (26)	Qualitative CSC	Any growth	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	NR/149	General inpatients	Suspected bloodstream infection
Jones et al., 1986 (56)	Qualitative CSC	Any growth	Primary bloodstream infection†	Blood culture	Prospective	NR/379	Patients with cancer	All catheters at removal
Nahass et al., 1990 (57)	Qualitative CSC	Any growth	Primary bloodstream infection†	Blood culture	Prospective	80/80	Surgical patients	All patients
Whitman and Boatman, 1995 (58)	Qualitative CSC	Any growth	Qualitative PBC and culture of catheter segment or reservoir material	Catheter segment	Retrospective	29/29	Patients with cancer, sickle-cell disease, and HIV infection	Suspected bloodstream infection
Maki et al., 1977 (25)	Semi-quantitative CSC	≥15 CFU	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	250/250	General inpatients	All catheters at removal
Maki et al., 1977 (64)	Semi-quantitative CSC	≥15 CFU	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	6/50	Patients with burns	All catheters at removal
Moyer et al., 1983 (70)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	67/67	Patients receiving total parenteral nutrition and patients with burns	All catheters at removal
Cooper and Hopkins, 1985 (59)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	224/330	Mostly patients in the ICU	All catheters at removal
Collignon et al., 1986 (66)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	440/780	Patients in the ICU	All catheters at removal
Jones et al., 1986 (56)	Semi-quantitative CSC	≥15 CFU	Primary bloodstream infection†	Blood culture	Prospective	NR/379	Patients with cancer	All catheters at removal
Collignon et al., 1987 (69)	Semi-quantitative CSC	≥15 CFU	Primary bloodstream infection†	Blood culture	Prospective	NR/322	NR	All catheters at removal
Rello et al., 1989 (72)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC or quantitative CSC	Catheter segment	Prospective	41/50	Patients with end-stage renal disease	All catheters at removal
Cercenado et al.,1990 (61)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	NR/139	General inpatients	All catheters at removal
Rello et al., 1991 (62)	Semi-quantitative CSC	≥15 CFU	Primary bloodstream infection†	Blood culture	Prospective	49/91	General inpatients	Suspected bloodstream infection
Aufwerber et al., 1991 (63)	Semi-quantitative CSC	≥15 CFU	Qualitative CSC and qualitative PBC	Catheter segment	Retrospective	453/542	Patients in the ICU	All catheters at removal
Raad et al., 1992 (65)	Semi-quantitative CSC	≥15 CFU	Catheter segment culture and qualitative PBC; clinical signs and symptoms of infection	Catheter segment	Prospective	153/313	General inpatients	All catheters at removal
Widmer et al., 1992 (67)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	NR/157	Patients in the ICU	All catheters at removal
Gutierrez et al., 1992 (60)	Semi-quantitative CSC	≥15 CFU	Semi-quantitative CSC or quantitative CSC and qualitative PBC	Catheter segment	Prospective	NR/98	General inpatients	Suspected bloodstream infection
Maki et al., 1996 (68)	Semi-quantitative CSC	≥15 CFU	Culture isolates of hub, infusate, or catheter segment and bloodstream infection by DNA subtyping	Blood culture	Prospective	NR/400	General inpatients	All catheters at removal
Kite et al., 1997 (32)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and quantitative CSC or semi-quantitative CSC	Catheter segment	Prospective	216/230	Surgical patients in the ICU	All catheters and suspected bloodstream infection
Kite et al., 1999 (37)	Semi-quantitative CSC	≥15 CFU	Quantitative PBC and semi-quantitative CSC or quantitative CSC	Catheter segment	Prospective	NR/112	Surgical patients	Suspected bloodstream infection
Snydman et al., 1982 (29)	Semi-quantitative CSC	≥15 CFU	Qualitative PBC and Qualitative CSC	Catheter segment	Prospective	100/69	Patients receiving total parenteral nutrition	All patients

Appendix Table—**Continued**

Study, Year (Reference)	Diagnostic Test Studied	Criteria for Positivity	Reference Standard Used	Basis of Reference Standard	Study Design	Patients/ Catheters or Infectious Episodes, *n/n*	Sample	Rationale for Performance of Diagnostic Test
Widmer et al., 2003 (71)	Semi-quantitative CSC	≥15 CFU	Semi-quantitative CSC or quantitative CSC and qualitative PBC	Catheter segment	Prospective	NR/1000	NR	All catheters at removal
Rello et al., 1989 (72)	Quantitative CSC	≥1000 CFU	Qualitative PBC and semi-quantitative CSC or quantitative CSC	Catheter segment	Prospective	41/50	Patients with end-stage renal disease	All catheters at removal
Cleri et al., 1980 (26)	Quantitative CSC	≥1000 CFU	Qualitative CSC and qualitative PBC	Catheter segment	Prospective	NR/149	General inpatients	Suspected bloodstream infection
Brun-Buisson et al., 1987 (27)	Quantitative CSC	≥1000 CFU	Qualitative PBC and qualitative CSC; no other focus of infection	Catheter segment	Prospective	231/331	Patients in the ICU	All catheters at removal
Rello et al., 1991 (62)	Quantitative CSC	≥1000 CFU	Primary bloodstream infection	Blood culture	Prospective	49/91	General inpatients	Suspected bloodstream infection
Kite et al., 1999 (37)	Quantitative CSC	≥1000 CFU	Quantitative PBC and semi-quantitative CSC or quantitative CSC	Catheter segment	Prospective	NR/112	Surgical patients	Suspected bloodstream infection
Gutierrez et al., 1992 (60)	Quantitative CSC	≥1000 CFU	Semi-quantitative CSC or quantitative PBC and qualitative PBC	Catheter segment	Prospective	NR/98	General inpatients	Suspected bloodstream infection
Kite et al., 1997 (52)	Quantitative CSC	≥1000 CFU	Qualitative PBC and quantitative PBC	Catheter segment	Prospective	NR/228	Surgical patients in the ICU	All catheters and suspected bloodstream infection
Sherertz et al., 1990 (28)	Quantitative CSC	≥1000 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Retrospective	104/216	Mostly patients in the ICU	Suspected bloodstream infection
Raad et al., 1992 (65)	Quantitative CSC	≥1000 CFU	Catheter segment culture, qualitative PBC, and clinical symptoms and signs of infection	Catheter segment	Prospective	153/313	General inpatients	All catheters at removal
Maki et al., 1996 (68)	Quantitative CSC	≥1000 CFU	Culture isolates of hub, infusate, or catheter segment and bloodstream infection concordant by DNA subtyping	Blood culture	Prospective	NR/400	General inpatients	All catheters at removal
Kelly et al., 1996 (73)	Quantitative CSC	≥1000 CFU	Qualitative PBC and qualitative CSC	Catheter segment	Retrospective and prospective	NR/405	General inpatients	All catheters at removal
Douard et al., 1999 (32)	Quantitative catheter septum and tip culture	>4-fold increase in growth from catheter blood compared with peripheral blood	No other focus of infection, and 1) purulence at the insertion site with positive exudates and PBCs or 2) signs and symptoms of sepsis with positive quantitative CSC and positive PBC	Catheter segment	Prospective	170/170	Immuno-compromised patients	All catheters at removal
Bjornson et al., 1982 (75)	Quantitative CSC	≥1000 CFU	Qualitative PBC and CSC	Catheter segment	Prospective	53/74	Patients receiving total parenteral nutrition	All catheters at removal
Widmer et al., 2003 (71)	Quantitative CSC	≥1000 CFU	Semi-quantitative CSC or quantitative CSC and qualitative PBC	Catheter segment	Prospective	NR/1000	NR	All catheters at removal
Snydman et al., 1982 (29)	IVD-drawn qualitative blood culture	Any growth	Qualitative PBC and Qualitative CSC	Catheter segment	Prospective	100/69	Patients receiving total parenteral nutrition	All patients
Bozzetti et al., 1984 (76)	IVD-drawn qualitative blood culture	Any growth	Semi-quantitative CSC and qualitative PBC	Catheter segment	Prospective	64/256	Patients with cancer	All patients
Paya et al., 1989 (77)	IVD-drawn qualitative blood culture	Any growth	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	44/52	Surgical patients in the ICU	Suspected bloodstream infection
Whitman and Boatman, 1995 (48)	IVD-drawn qualitative blood culture	Any growth	Semi-quantitative CSC and qualitative PBC	Catheter segment	Retrospective	29/29	Patients with cancer, sickle-cell disease, and HIV infection	Suspected bloodstream infection
Raucher et al., 1984 (78)	IVD-drawn qualitative blood culture	>5:1	Peripheral qualitative blood culture and catheter blood culture	Blood culture	Prospective	28/30	Children	Suspected bloodstream infection

Appendix Table—**Continued**

Study, Year (Reference)	Diagnostic Test Studied	Criteria for Positivity	Reference Standard Used	Basis of Reference Standard	Study Design	Patients/ Catheters or Infectious Episodes, *n/n*	Sample	Rationale for Performance of Diagnostic Test
Capdevila et al., 1992 (31)	IVD-drawn qualitative blood culture	Any growth	Qualitative PBC and semi-quantitative CSC; no other source; recovery after catheter removal	Catheter segment	Prospective	64/107	NR	Suspected bloodstream infection
Moyer et al., 1983 (70)	IVD-drawn qualitative blood culture	Any growth	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	67/67	Patients receiving total parenteral nutrition and patients with burns	All catheters at removal
Paya et al., 1989 (77)	IVD-drawn quantitative blood culture	Any growth	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	44/52	Surgical patients in the ICU	Suspected bloodstream infection
Snydman et al., 1982 (29)	IVD-drawn quantitative blood culture	>15 CFU	Qualitative PBC and qualitative CSC	Catheter segment	Prospective	100/69	Patients receiving total parenteral nutrition	All patients
Raucher et al., 1984 (78)	IVD-drawn quantitative blood culture	>5:1	Qualitative PBC and catheter blood culture	Blood culture	Prospective	28/30	Children	Suspected bloodstream infection
Capdevila et al., 1992 (31)	IVD-drawn quantitative blood culture	>100 CFU	Qualitative PBC and semi-quantitative CSC; no other source; recovery after catheter removal	Catheter segment	Prospective	64/107	NR	Suspected bloodstream infection
Moyer et al., 1983 (70)	IVD-drawn quantitative blood culture	≥25 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	67/67	Patients receiving total parenteral nutrition and patients with burns	All catheters at removal
Franklin et al., 2004 (91)	IVD-drawn quantitative blood culture	≥100 CFU	Paired quantitative blood culture	Blood culture	Retrospective	241/241	Children with cancer	Suspected bloodstream infection
Catton et al., 2002 (94)	IVD-drawn quantitative blood culture	>100 CFU	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	205/205	Surgical patients	Suspected bloodstream infection
Flynn et al., 1988 (34)	Paired lysis–centrifugation‡ quantitative blood culture	>5-fold increase in growth from catheter compared with periphery	Qualitative PBC and qualitative catheter blood culture	Blood culture	Prospective	13/13	Children	Suspected bloodstream infection
Sanchez-Conde et al., 2003 (79)	Paired lysis–centrifugation‡ quantitative blood culture	>5-fold increase in growth from catheter compared with periphery	Qualitative PBC and CSC	Catheter segment	Prospective	145/145	Adults	Suspected bloodstream infection
Douard et al., 1991 (74)	Paired quantitative blood culture	>5-fold	Positive paired quantitative blood cultures	Blood culture	Prospective	NR/53	Children with hematologic or oncologic illness	Suspected bloodstream infection
Douard et al., 1994 (33)	Paired quantitative blood culture	>3:1	Positive PBC and CSCs	Catheter segment	Prospective	58/58	Medical and surgical patients in the ICU	Suspected bloodstream infection
Mosca et al., 1987 (80)	Paired lysis–centrifugation‡ quantitative blood culture	>5-fold	Clinical follow-up	Other	Prospective	25/26	General inpatients	Suspected bloodstream infection
Paya et al., 1989 (77)	Paired lysis–centrifugation‡ quantitative blood culture	>30 CFU compared with peripheral sample	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	44/52	Surgical patients in the ICU	Suspected bloodstream infection
Fortun et al., 2000 (81)	Paired lysis–centrifugation‡ quantitative blood culture	>5:1	Qualitative PBC and semi-quantitative CSC	Catheter segment	Prospective	NR/118	General inpatients	All catheters at removal
Capdevila et al., 1992 (31)	Paired quantitative blood culture	>4:1	Qualitative PBC and semi-quantitative CSC; no other source of infection; recovery after catheter removal	Catheter segment	Prospective	64/107	Patients in the ICU	Suspected bloodstream infection
Raucher et al., 1984 (78)	Paired quantitative blood culture	>5:1	Qualitative PBC and catheter blood culture	Blood culture	Prospective	28/30	Children	Suspected bloodstream infection

Appendix Table—**Continued**

Study, Year (Reference)	Diagnostic Test Studied	Criteria for Positivity	Reference Standard Used	Basis of Reference Standard	Study Design	Patients/ Catheters or Infectious Episodes, *n/n*	Sample	Rationale for Performance of Diagnostic Test
Douard et al., 1999 (32)	Paired lysis–centrifugation‡ quantitative blood culture	>4-fold increase in growth from catheter-drawn blood compared with peripherally drawn blood	No other focus of infection, and 1) purulence at the insertion site with positive exudates and PBCs or 2) signs and symptoms of sepsis with positive quantitative CSC and positive PBC	Catheter segment	Prospective	170/170	Immuno-compromised patients	All catheters at removal
Blot et al., 1999 (35)	Differential time to positivity	>2 h	Qualitative PBC and quantitative CSC	Catheter segment	Prospective	87/93§	General inpatients	Suspected bloodstream infection
Malgrange et al., 2001 (83)	Differential time to positivity	>2 h	Qualitative PBC and quantitative CSC	Catheter segment	Prospective	NR/98§	Patients with cancer	Suspected bloodstream infection
Rjinders et al., 2001 (84)	Differential time to positivity	>2 h	Qualitative PBC and quantitative CSC	Catheter segment	Prospective	10/10	Medical and surgical patients in the ICU	Suspected bloodstream infection
Blot et al., 1998 (82)	Differential time to positivity	>2 h	Qualitative PBC and quantitative CSC	Catheter segment	Retrospective	NR/42§	General inpatients	Suspected bloodstream infection
Gaur et al., 2002 (89)	Differential time to positivity	>2 h	Paired quantitative blood culture	Blood culture	Prospective	NR/28§	Children with cancer	Suspected bloodstream infection
Mermel et al., 1998 (85)	Differential time to positivity	>2 h	Clinical definition	Other	Retrospective	36/31	General inpatients	Suspected bloodstream infection
Raad et al., (90)	Differential time to positivity	>2 h	No other focus of infection; signs and symptoms; and semi-quantitative catheter tip culture with PBC or paired quantitative blood culture, or both	Blood culture	Prospective	201/191	Adults with cancer	Suspected bloodstream infection
Seifert et al., 2003 (36)	Differential time to positivity	>2 h	Paired quantitative blood culture, DNA subtyping, and quantitative CSC	Blood culture	Prospective	51/51	Patients with neutropenia	Suspected bloodstream infection
Sanchez-Conde et al., 2003 (79)	Differential time to positivity	>2 h	Qualitative PBC and quantitative CSC	Blood culture	Prospective	145/145	Adults	Suspected bloodstream infection
Rushforth et al., 1993 (86)	Acridine orange leukocyte cytospin	Any growth	Paired quantitative blood culture	Blood culture	Prospective	51/95§	Infants	Suspected bloodstream infection
von Baum et al., 1998 (87)	Acridine orange leukocyte cytospin	Any growth	Semi-quantitative CSC and qualitative PBC	Catheter segment	Prospective	14/14	Adults in the ICU	Random sampling of both suspected bloodstream infection and not bloodstream infection; data obtained from subgroup analysis
Kite et al., 1999 (40)	Acridine orange leukocyte cytospin	Any growth	Quantitative PBC and semi-quantitative CSC or quantitative CSC	Catheter segment	Prospective	NR/112	Surgical patients	Suspected bloodstream infection
Tighe et al., 1996 (36)	Acridine orange leukocyte cytospin	Any growth	Semi-quantitative CSC and qualitative PBC	Catheter segment	Prospective	50/50	General inpatients	Suspected bloodstream infection
Bong et al., 2003 (87)	Acridine orange leukocyte cytospin	Any growth	Semi-quantitative CSC and qualitative PBC	Catheter segment	Prospective	50/50	Surgical patients	Suspected bloodstream infection

* CFU = colony-forming units; CSC = catheter segment culture; ICU = intensive care unit; IVD = intravascular device; NR = not reported; PBC = peripheral blood culture.
† Presence of bacteremia while the catheter is in place and no other probable source of bacteremia.
‡ Isolator system (Wampole Laboratories, Cranbury, New Jersey).
§ Infectious episodes.