

Chlorhexidine Compared with Povidone-Iodine Solution for Vascular Catheter–Site Care: A Meta-Analysis

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Purpose: Bloodstream infections related to use of catheters, particularly central-line catheters, are an important cause of patient morbidity, mortality, and increased health care costs. This study evaluated the efficacy of skin disinfection with chlorhexidine gluconate compared with povidone-iodine solution in preventing catheter-related bloodstream infection.

Data Sources: Multiple computerized databases (1966 to 2001), reference lists of identified articles, and queries of principal investigators and antiseptic manufacturers.

Study Selection: Randomized, controlled trials comparing chlorhexidine gluconate with povidone-iodine solutions for catheter-site care.

Data Extraction: Using a standardized form, two reviewers abstracted data on study design, patient population, intervention, and incidence of catheter-related bloodstream infection from all included studies.

Data Synthesis: Eight studies involving a total of 4143 catheters met the inclusion criteria. All studies were conducted in a hospital setting, and various catheter types were used. The summary risk ratio for catheter-related bloodstream infection was 0.49 (95% CI, 0.28 to 0.88) in patients whose catheter sites were disinfected with chlorhexidine gluconate instead of povidone-iodine. Among patients with a central vascular catheter, chlorhexidine gluconate reduced the risk for catheter-related bloodstream infection by 49% (risk ratio, 0.51 [CI, 0.27 to 0.97]).

Conclusions: These results suggest that incidence of bloodstream infections is significantly reduced in patients with central vascular lines who receive chlorhexidine gluconate versus povidone-iodine for insertion-site skin disinfection. Use of chlorhexidine gluconate is a simple and effective means of reducing vascular catheter-related infections.

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Intravascular catheters are commonly used in caring for hospitalized patients but can lead to serious infectious complications (1). Catheter-related bloodstream infection is associated with increased morbidity, mortality, length of hospitalization, and medical costs (2–6). Use of an antiseptic solution for skin disinfection at the catheter insertion site helps prevent catheter-related infections. Povidone-iodine solution is the most commonly used agent for this purpose (7, 8).

Recently, several studies have compared the efficacy of povidone-iodine with that of chlorhexidine gluconate solutions for reducing vascular catheter-related infections (7, 9–14; Knasinski V, Maki DG. A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters [Presented paper]. San Diego: National Association of Vascular Access Network Conference; 2000). Unfortunately, because few clinical events have been observed in individual studies, it remains unclear which antiseptic solution is best, both statistically and clinically, for reducing the risk for catheter-related bloodstream infection, particularly in patients with central-line catheters.

We sought to aid clinical decision making by evaluating the effectiveness of chlorhexidine gluconate versus povidone-iodine as a skin disinfectant for catheter-site care. We performed a meta-analysis of all available published and unpublished studies comparing chlorhexidine gluconate with povidone-iodine solution for vascular catheter–site care.

METHODS

Study Selection

We manually searched Index Medicus (1960 to 1965) and electronically searched MEDLINE (1966 to 2001), CINAHL: Nursing and Allied Health (1982 to 2001), Doctoral Dissertation Abstracts (1861 to 2001), International Pharmaceutical Abstracts (1970 to 2001), EMBASE, Lexis–Nexus, Web of Sciences, and Cochrane Library databases for publications in any language. For our search strategy, we used the Medical Subject Headings *chlorhexidine* and *catheterization* and the exploded key words *chlorhexidine* and *catheter*. We restricted the searches to clinical trials. To ensure that our search would be thorough, we consulted a research librarian at the University of Washington. To identify

additional original studies, we reviewed the reference lists of the retrieved articles and any identified review articles. Studies presented at recent scientific meetings in the area of infection control were also identified by reviewing meeting programs and published meeting proceedings and by attending medical meetings on related topics. We contacted the manufacturer of chlorhexidine gluconate solution, the corresponding authors of relevant studies, and experts in the field to inquire about possible additional studies.

To be included in the meta-analysis, a study needed 1) to be a randomized trial comparing any type of chlorhexidine gluconate solution with a povidone-iodine solution for vascular catheter-site care and 2) to report the incidence of catheter colonization or catheter-related bloodstream infection with sufficient data to calculate the risk ratio.

Outcome Measures

The primary outcome was catheter-related bloodstream infection, which we defined as isolation of the same organism (that is, identical species with the same antibiograms) from a peripheral blood culture and a semiquantitative or quantitative culture of a catheter segment. Our secondary outcome, catheter colonization, was defined as significant growth of microorganisms from a catheter segment, according to quantitative (>1000 colony-forming units [CFUs] per mL) or semiquantitative (>15 CFU) culture techniques (15, 16).

Data Extraction

Using a standardized data form, two investigators independently abstracted data on the size of the study sample, type of patient population, type of vascular catheter used, type of antiseptic used, anatomic site of insertion, use of catheter exchange with guide wire, concurrent use of other interventions, and incidence of catheter colonization and catheter-related bloodstream infection. We also evaluated the following methodologic components of each study: randomization procedure, extent of blinding, and description of eligible participants. The authors of studies that did not contain sufficient data were contacted for additional information.

Context

Intravascular catheter-related bloodstream infection is an important and potentially avoidable cause of morbidity.

Various antiseptic solutions for skin disinfection and catheter-site care may help prevent catheter-related infections.

Contribution

This article summarizes data from eight randomized trials that compared antiseptic solutions.

Approximately 1% of the patients with chlorhexidine gluconate disinfectant developed bloodstream infections from intravascular catheters. In the patients with disinfection by povidone-iodine, the rate was 2% (risk ratio, 0.49 [95% CI, 0.28 to 0.88]).

Implications

Chlorhexidine gluconate is more effective than povidone-iodine for intravascular catheter-site care. It is also more expensive.

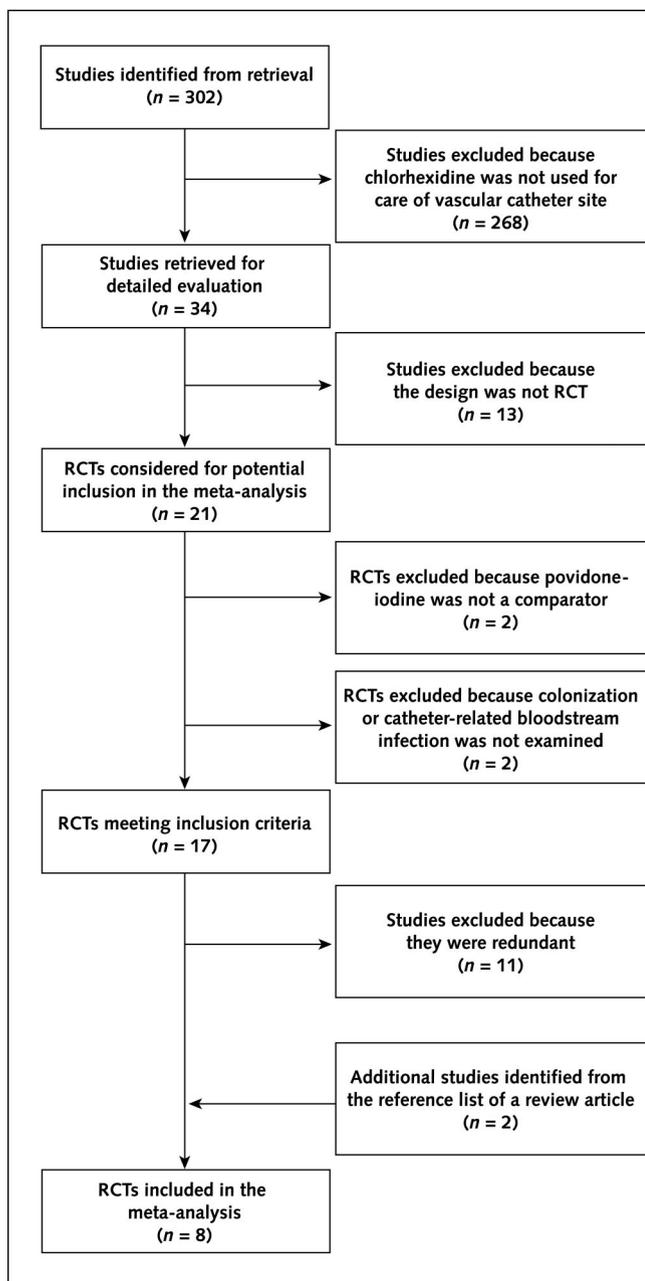
—The Editors

Statistical Analysis

We separately analyzed the incidences of catheter colonization and catheter-related bloodstream infection. The summary risk ratios and 95% CIs were calculated by using the DerSimonian and Laird method under a random-effects model (17). A statistical test of heterogeneity was performed by using the Mantel-Haenszel method (18). To explore potential clinical sources of heterogeneity, we conducted sensitivity analyses according to characteristics of the study, the study participants, the types of catheters used, outcome definitions, and concentrations of antiseptics used. We explored publication bias using the funnel-plot method by graphing the effect size of trials on the horizontal axis and the number of participants in each trial on the vertical axis (19); asymmetry in the funnel plot suggested publication bias.

Because some studies allowed patients to receive more than one vascular catheter during the study period, the within-patient correlation could underestimate the standard error of the effect measure. To investigate this effect, we inflated the variance of the risk ratio for each study by multiplying it by the average number of catheters per patient (20). To perform all statistical analyses, we used Stata software, version 6.0 (Stata Corp. College Station, Texas), by employing the command "METAN."

Figure 1. Trial flow depicting the selection process of studies included in the meta-analysis.



RCT = randomized, controlled trial.

RESULTS

Study Selection

We located 302 articles from our manual and computerized searches (Figure 1). Reviews of the titles and abstracts from the computerized search, followed by re-

view of the full manuscripts of potentially relevant articles, identified 6 published studies that met our inclusion criteria. Of the 296 remaining studies, 285 were excluded because chlorhexidine gluconate was not used for catheter-site care ($n = 268$), use of the disinfectants was not determined by random allocation ($n = 13$), povidone-iodine was not used as a comparator ($n = 2$), or colonization or catheter-related bloodstream infection was not recorded ($n = 2$). The other 11 excluded studies were duplicate studies retrieved from different databases. In addition to the 6 studies identified from searches, 1 published abstract (9) and 1 published study (10) were identified from the reference list of a review article (21). Thus, our meta-analysis comprised 8 total studies. Studies were reviewed by two investigators, and there were no discrepancies in the abstracted data.

Study Characteristics

Table 1 shows the characteristics of the eight included studies. These trials used 4143 catheters (1493 central venous, 1361 peripheral venous, 704 peripheral arterial, 395 pulmonary arterial, 75 peripherally inserted central venous, 62 introducer sheaths, and 53 hemodialysis). Five studies included only patients from intensive care units (7, 9, 11, 12, 14); three studies included patients from any unit in the hospital (10, 13; Knasinski V, Maki DG [Presented paper]). One study was a multicenter clinical trial (10). Among the included studies that reported patient age, the average age ranged from 50 to 65 years (7, 10–12, 14). The mean duration of catheterization for the chlorhexidine gluconate and povidone-iodine groups was similar in all studies that provided this information, except one in which the chlorhexidine gluconate group was catheterized longer (9.9 vs. 5.9 days) (14). There was no significant difference in the anatomic sites (such as subclavian or femoral) in which catheters were inserted between the chlorhexidine gluconate and povidone-iodine groups. One study allowed catheter exchange via a guide wire (7). Only one study noted adverse effects from the use of either antiseptic solution: Maki and colleagues (7) found erythema at the insertion site in 28.3% of catheters in the povidone-iodine group and in 45.3% of catheters in the chlorhexidine gluconate group ($P < 0.001$). However, there was no statistically significant difference in ery-

thema among these two groups and patients whose sites were disinfected with alcohol (7).

The included studies used several formulations of chlorhexidine gluconate. Five studies (10, 13, 14; Knasinski V, Maki DG [Presented paper]) used an alcoholic solution, and three studies (7, 9, 11) used an aqueous solution. All studies used 10% povidone-iodine solution for the control group. However, only one study specified the sequence of applications of 70% alcohol and 10% povidone-iodine (13). Five studies clearly described their procedures for care of the catheter site (7, 10–12, 14); in these studies, the dressing was changed and the insertion site was typically cleansed every 48 to 72 hours (7). Sterile gauze was used for dressing in three studies (7, 11, 14); meanwhile, one study used semioclusive dressing (12) and another study used opaque and transparent dressings (10). Four studies (10, 11, 13; Knasinski V, Maki DG [Presented paper]) specified that antibiotic ointments were not used; three studies (10, 13; Knasinski V, Maki DG [Presented paper]) specifically indicated that no antimicrobial-impregnated catheters were allowed.

Five studies (7, 9, 13, 14; Knasinski V, Maki DG [Presented paper]) cultured intravascular catheter segments by using the roll-plate semiquantitative method (16), two studies (11, 12) used the quantitative culture method (15), and one study defined catheter colonization by either method (10). All studies evaluating catheter-related bloodstream infection as an outcome required the recovery of the same microbial species from both the catheter segment and a blood culture. In addition, two studies (14; Knasinski V, Maki DG [Presented paper]) required confirmation by molecular subtyping, five studies (7–10, 14; Knasinski V, Maki DG [Presented paper]) required no other sources of infection, and five (7, 9–12) required the presence of clinical signs or symptoms of infection (Table 1). All studies provided sufficient information to calculate the incidence of catheter colonization and catheter-related bloodstream infection except for the study by LeBlanc and Cobett (13), which provided data on catheter colonization only.

The unit of randomization was the patient in all included studies, except for two studies that used random assignment based on catheters (9, 12). For these latter two studies, the average catheter-to-patient ratio (that is, the number of catheters inserted during hospitalization in a particular patient) was 1.83 and 2.41,

respectively. Four studies reported the randomization procedure (10, 11, 13, 14), which was found adequate on reviewer assessment. Only one study blinded investigators to antiseptic solution being used (13). Patient eligibility criteria were clearly described in all studies except three (9, 13; Knasinski V, Maki DG [Presented paper]).

Catheter-Related Bloodstream Infection and Catheter Colonization

Risk for catheter colonization and catheter-related bloodstream infection were significantly lower in the chlorhexidine gluconate group than in the povidone-iodine group (Table 2). The summary risk ratio for catheter colonization for all vascular catheters in the chlorhexidine gluconate compared with the povidone-iodine group was 0.49 (95% CI, 0.31 to 0.71). The summary risk ratio for catheter-related bloodstream infection for all vascular catheters was 0.49 (CI, 0.28 to 0.88), indicating a significantly reduced risk in patients using chlorhexidine gluconate (Figure 2). The pooled proportions of colonization and catheter-related bloodstream infection in the povidone-iodine group were 0.139 (CI, 0.087 to 0.191) and 0.0216 (CI, 0.0124 to 0.0307), respectively. The absolute risk reduction was 7.1% for colonization and 1.1% for catheter-related bloodstream infection. The test for heterogeneity of treatment effect was significant for catheter colonization ($P < 0.001$) but not for catheter-related bloodstream infection ($P > 0.2$). There was no evidence of publication bias, as indicated by the symmetrical shape of the funnel plot.

Sensitivity Analyses

Sensitivity analyses performed to investigate possible sources of heterogeneity in the studies examining catheter colonization showed that the trial by Humar and colleagues (14) was the predominant source. This was the only study in which the incidence of catheter colonization in the chlorhexidine gluconate group was higher than that in the povidone-iodine group. The increased risk for catheter colonization in the chlorhexidine gluconate group probably resulted from the longer mean duration of catheterization compared with the povidone-iodine group (9.9 vs. 5.2 days) (14) among patients whose catheter segment was available for a semiquantitative culture. When this study was excluded from

Table 1. Characteristics of Studies Comparing Chlorhexidine Gluconate Solutions with Povidone-Iodine Solutions for Vascular Catheter-Site Care*

Study (Reference), Year	Antiseptic CHG Solution	Patient Population	Catheters and Patients, n/n		Mean Catheter Duration, d	
			CHG Group	Povidone-Iodine Group†	CHG Group	Povidone-Iodine Group†
Maki et al. (7), 1991	2% aqueous	ICU	214/214	227/227	5.3	5.3
Sheehan et al. (9), 1993	2% aqueous	ICU	169/94	177/95	NA	NA
Meffre et al. (10), 1995‡	0.5% alcohol	Any hospital unit	568/568	549/549	1.6	1.6
Mimoz et al. (11), 1996	Biseptine§	ICU	170/NA	145/NA	4.5	3.9
Legras et al. (12), 1997	0.5% alcohol	ICU	208/88	249/102	10	10
LeBlanc and Cobett (13), 1999‡	0.5% alcohol	Any hospital unit	83/83	161/161	1.6	1.7
Humar et al. (14), 2000	0.5% alcohol	ICU	193/193	181/181	5.3	6.3
Knasinski and Maki, 2000¶¶	1% alcohol	Any hospital unit	349/349	500/500	NA	NA

* CFU = colony-forming unit; CHG = chlorhexidine gluconate; ICU = intensive care unit; NA = not available.

† All studies used 10% povidone-iodine solution.

‡ Author provided additional information.

§ Biseptine (Nicholas, Gaillard, France) consists of 0.25% CHG, 0.025% benzalkonium chloride, and 4% benzyl alcohol.

¶ Required one of the following symptoms: fever, erythema, heat at the site, pain.

¶¶ Knasinski V, Maki DG. A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters [Presented paper]. San Diego: National Association of Vascular Access Network Conference; 2000.

our analysis, the *P* value for the test of heterogeneity increased from less than 0.001 to greater than 0.2. Analysis of the other seven studies produced a summary risk ratio for catheter colonization of 0.43 (CI, 0.33 to 0.55). After the study by Humar and colleagues (14) was excluded, the summary risk ratio for catheter-related bloodstream infection (0.45 [CI, 0.23 to 0.85]) was similar to that found when all studies were included. Accounting for increased variance due to possible within-patient correlation led to similar point estimates and CIs for catheter colonization (risk ratio, 0.49 [CI, 0.31 to 0.78]) and catheter-related bloodstream infection (risk ratio, 0.50 [CI, 0.28 to 0.91]).

In all subgroup analyses, the overall relative risk reductions with chlorhexidine gluconate compared with povidone-iodine remained approximately 50% for cath-

eter colonization and for catheter-related bloodstream infection. When we excluded the study that allowed catheter exchange over a guide wire, the results (risk ratio, 0.53 [CI, 0.33 to 0.85] for catheter colonization and 0.54 [CI, 0.29 to 0.98] for catheter-related bloodstream infection) were still consistent with our main findings. Analysis of studies using chlorhexidine alcohol solutions produced a summary risk ratio of 0.57 (CI, 0.35 to 0.94) for catheter colonization and 0.52 (CI, 0.28 to 0.96) for catheter-related bloodstream infection. When only central vascular catheters (that is, non-tunneled central venous catheters, pulmonary arterial catheters, and peripherally inserted central venous catheters) were included in the analysis, the results were similar (summary risk ratio, 0.52 [CI, 0.29 to 0.95] for catheter colonization and 0.51 [CI, 0.27 to 0.97] for

Table 1—Continued

Outcome Definitions	
Catheter Colonization	Catheter-Related Bloodstream Infection
Semiquantitative (>15 CFU)	Same organism or species matched between blood and catheter segment culture; no other source of infection; clinical symptoms of bloodstream infection
Semiquantitative (>15 CFU)	Same organism or species matched between blood and catheter segment culture; no other source of infection; clinical symptoms of bloodstream infection
Semiquantitative (>15 CFU) or quantitative (>10 ³ CFU/mL)	Local or clinical symptoms of bloodstream infection or same organism or species matched between blood and catheter segment culture; no other source of infection
Quantitative (>10 ³ CFU/mL)	Same organism or species matched between blood and catheter segment culture; clinical symptoms of bloodstream infection
Quantitative (>10 ³ CFU/mL)	Same organism or species matched between blood and catheter segment culture; clinical symptoms of bloodstream infection
Semiquantitative (>15 CFU)¶	NA
Semiquantitative (>15 CFU)	Same organism or species matched between blood and catheter segment culture; same organism confirmed by molecular subtyping; no other source of infection
Semiquantitative (>15 CFU)	Same organism or species matched between blood and catheter segment culture; same organism confirmed by molecular subtyping; no other source of infection

catheter-related bloodstream infection). Likewise, an analysis including only noncentral catheters revealed similar results (risk ratio, 0.39 [CI, 0.21 to 0.71] for catheter colonization and 0.45 [CI, 0.05 to 3.77] for catheter-related bloodstream infection). In studies that included only patients hospitalized in intensive care units, the summary risk ratio for disinfection by chlorhexidine gluconate was 0.53 (CI, 0.27 to 1.03) for catheter colonization and 0.52 (CI, 0.23 to 1.17) for catheter-related bloodstream infection.

Analysis of studies that required clinical symptoms (for the definition of catheter-related bloodstream infection or as the indication for drawing blood cultures) yielded a summary risk ratio for catheter-related bloodstream infection of 0.53 (CI, 0.22 to 1.27). In the studies for which catheter-related bloodstream infection required identical antibiograms or molecular subtyping, the summary risk ratio for chlorhexidine gluconate was 0.52 (CI, 0.27 to 1.02). In an analysis of the studies in which absence of other sources of infection was part of

the definition of catheter-related bloodstream infection, the summary risk ratio was 0.50 (CI, 0.26 to 0.96).

DISCUSSION

Use of chlorhexidine gluconate solution for care of catheter sites is significantly more effective than use of povidone-iodine solution for preventing vascular catheter-related infections. We estimate that for every 1000 catheter sites disinfected with chlorhexidine gluconate rather than povidone-iodine, 71 episodes of catheter colonization and 11 episodes of catheter-related bloodstream infection would be prevented.

The summary risk reduction for catheter-related bloodstream infection in the main analysis and the sensitivity analyses suggests that chlorhexidine gluconate solution reduces the risk for catheter-related bloodstream infection by approximately 50%. This reduction remained statistically significant even when only central vascular catheters were included. The implications of such a reduction are substantial because patients requiring central vascular catheters are typically at high risk for this costly complication (22–24). The magnitudes of the risk reductions in the subgroup analyses were similar to those in the main analysis. The failure to find a significant difference in some subgroup analyses is probably due to the low incidence of clinical events (for example, with peripheral lines) and small sample sizes.

Our study has several limitations that stem from the designs of the individual trials. First, in studies with multiple catheters per patient, the effects measured for the same patient are likely to be correlated. The resulting within-patient correlation causes an underestimation of the standard error of the benefits of chlorhexidine gluconate solution. A sensitivity analysis in which the variance of the studies was increased affected the results only slightly.

Second, several types of chlorhexidine gluconate solution were used in the individual trials, including 0.5% or 1% chlorhexidine gluconate alcohol solution and 0.5% or 2% chlorhexidine gluconate aqueous solution. All of these solutions provide a concentration of chlorhexidine gluconate that is higher than the minimal inhibitory concentrations for most nosocomial bacteria and yeast (7). Subset analyses of aqueous and nonaqueous solutions showed similar effect sizes, but only the subset analysis of the five studies that used alcoholic

Table 2. Results of Studies Comparing Chlorhexidine Gluconate Solutions with Povidone-Iodine Solutions for Vascular Catheter-Site Care*

Study (Reference), Year	Catheter Colonization			Catheter-Related Bloodstream Infection		
	Proportion of Positive Cultures		RR (95% CI) Using CHG Solution†	Proportion of Patients with Infection		RR (95% CI) Using CHG Solution†
	CHG Group	Povidone-Iodine Group		CHG Group	Povidone-Iodine Group	
	n/n (%)		n/n (%)			
Maki et al. (7), 1991	5/214 (2.3)	21/227 (9.2)	0.25 (0.10–0.66)	1/214 (0.4)	6/227 (2.6)	0.18 (0.02–1.46)
Sheehan et al. (9), 1993	3/169 (1.8)	12/177 (6.8)	0.22 (0.06–0.75)	1/169 (0.6)	1/177 (0.6)	1.05 (0.07–16.61)
Meffre et al. (10), 1995‡	9/568 (1.6)	22/549 (4.0)	0.40 (0.18–0.85)	3/568 (0.5)	3/549 (0.5)	0.97 (0.20–4.77)
Mimoz et al. (11), 1996	12/170 (7.1)	24/145 (16.6)	0.43 (0.22–0.82)	3/170 (1.8)	4/145 (2.8)	0.64 (0.15–2.81)
Legras et al. (12), 1997	19/208 (9.1)	31/249 (12.4)	0.73 (0.43–1.26)	0/208 (0.0)	4/249 (1.6)	0.13 (0.01–2.45)
LeBlanc and Cobett (13), 1999‡	6/83 (7.2)	23/161 (16.1)	0.49 (0.31–0.77)	–	–	–
Humar et al. (14), 2000	36/116 (31.0)	27/116 (23.3)	1.33 (0.87–2.04)	4/193 (2.1)	5/181 (2.8)	0.75 (0.20–2.75)
Knasinski and Maki, 2000§	33/349 (9.5)	127/500 (25.4)	0.37 (0.26–0.53)	5/349 (1.4)	20/500 (4.0)	0.36 (0.14–0.95)
All studies			0.49 (0.31–0.71)			0.49 (0.28–0.88)
All studies excluding Humar et al.			0.43 (0.33–0.55)			0.45 (0.23–0.85)

* CHG = chlorhexidine gluconate; RR = risk ratio.

† Risk ratio for use of chlorhexidine gluconate versus povidone-iodine.

‡ Author provided additional information.

§ Knasinski V, Maki DG. A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters [Presented paper]. San Diego: National Association of Vascular Access Network Conference; 2000.

solution produced a statistically significant reduction in catheter-related bloodstream infection. Because few studies used chlorhexidine gluconate aqueous solution, the lack of a significant difference seen for this solution compared with povidone-iodine solution may be a result of inadequate statistical power.

Third, several studies defined catheter-related bloodstream infection differently. Some studies required the presence of clinical symptoms of bloodstream infection (7, 9–12) or the absence of other sources of infection (7, 9, 10, 14; Knasinski V, Maki DG [Presented paper]), whereas other studies used molecular subtyping techniques to determine whether the organisms isolated were identical (14; Knasinski V, Maki DG [Presented paper]). All trials, however, required isolation of the same organism or microbial species from a peripheral blood culture and a culture of a catheter segment.

Fourth, none of the eight included studies reported strategies to distinguish true bacteremia from blood culture contamination. Given that coagulase-negative staphylococci are the most common contaminants (25), it is possible that contaminated specimens may have been falsely viewed as true bacteremia. In the studies that reported the organism causing catheter-related bloodstream infection (7, 12, 14), gram-positive cocci

caused most infections (62%); 29% of the organisms were specifically coagulase-negative staphylococci. If it is assumed that the same procedures were used to obtain a peripheral blood culture in the chlorhexidine gluconate and povidone-iodine groups, the rate of misclassification would be similar in both groups.

The heterogeneity identified in the analysis of catheter colonization implies that these trials may have measured different treatment effects for the povidone-iodine and chlorhexidine gluconate solutions. The source of the heterogeneity, however, arose mainly from the study by Humar and colleagues (14), probably as a result of the longer mean duration of catheterization in the chlorhexidine gluconate group.

Publication bias seriously threatens the methodologic validity of meta-analyses (18). To minimize this bias, we exhaustively searched for published and unpublished studies in any language. If publication bias were present, the smaller trials would tend to report a greater preventive effect because smaller trials with significant results are more likely to be published than are smaller studies with nonsignificant results. Our analysis, however, revealed no evidence of such a bias.

The superiority of chlorhexidine gluconate for catheter-site care has several potential explanations. First,

blood, serum, and other protein-rich biomaterials can deactivate the microbicidal effect of povidone-iodine (26, 27) but not chlorhexidine gluconate (28, 29). Second, the residual effect of chlorhexidine gluconate, defined as the long-term antimicrobial suppressive activity, is prolonged (at least 6 hours) (30, 31), while that of povidone-iodine is minimal (32). The superiority of chlorhexidine gluconate compared with povidone-iodine in reducing the colony counts of coagulase-negative staphylococci has been previously shown in a study of disinfection of peritoneal dialysis catheter sites (33). Because most vascular catheter-related infections are caused by gram-positive cocci, the superior bactericidal effect of chlorhexidine gluconate against these organisms is likely to be clinically important.

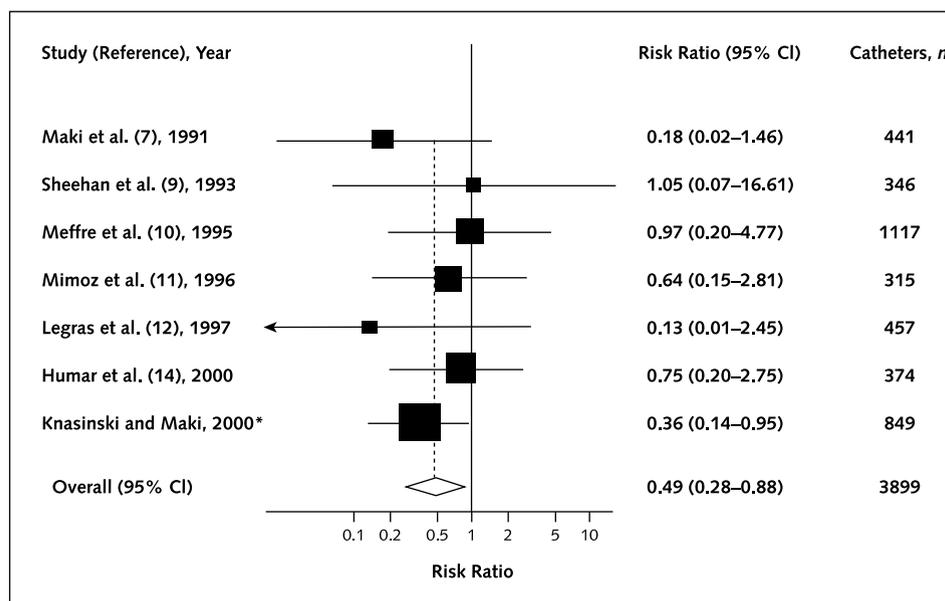
Two additional issues should be considered regarding the use of chlorhexidine gluconate for catheter-site care. Hypersensitivity reactions have been reported with use of central venous catheters impregnated by chlorhexidine-silver sulfadiazine and with use of chlorhexidine gluconate for bathing (34–38). No hypersensitivity reactions were reported by the studies in our meta-anal-

ysis; however, clinicians should be alert to this and other potential side effects, including increased erythema, which one study (7) reported. Bacterial resistance is another potential concern, but very few reports of resistance to chlorhexidine gluconate exist despite its widespread use for several decades (39).

Our results are somewhat generalizable. We combined clinical trials with different patient populations; different concentrations and types of chlorhexidine gluconate solution; and different types of vascular catheters inserted, on average, for 1 to approximately 10 days. Thus, our results may apply to most hospitalized patients in the United States and similar health care settings. We cannot address, however, the role of chlorhexidine gluconate in preventing catheter-related bloodstream infection in patients who are catheterized for an average of longer than 10 days or the potential additional benefit of chlorhexidine gluconate when an antimicrobial catheter is used (40, 41).

Considering the progressive accumulation of studies over the past decade supporting the efficacy of chlorhexidine gluconate in reducing catheter colonization,

Figure 2. Analysis of catheter-related bloodstream infection in studies comparing chlorhexidine gluconate and povidone-iodine solutions for care of vascular catheter sites.



The diamond indicates the summary risk ratio and 95% CI. Studies are ordered chronologically. The size of squares is proportional to the reciprocal of the variance of the studies. For the test for heterogeneity of treatment effect, $P > 0.2$. *Knasinski V, Maki DG. A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters [Presented paper]. San Diego: National Association of Vascular Access Network Conference; 2000.

why has this disinfectant not been more widely used for catheter-site care? One reason may be the previous lack of clear clinical evidence demonstrating the superiority of chlorhexidine gluconate versus povidone-iodine in reducing catheter-related bloodstream infections in patients with central vascular catheters. Another reason may be the higher cost of chlorhexidine gluconate. However, although chlorhexidine gluconate is approximately twice as expensive as povidone-iodine, the absolute difference is relatively small (approximately \$0.92 vs. \$0.41 for a quantity sufficient to prepare an insertion site for a central venous catheter). Although our meta-analysis suggests that the use of chlorhexidine gluconate is likely to be cost-effective, or even cost saving, a formal economic evaluation is needed.

We found that the use of chlorhexidine gluconate rather than povidone-iodine can reduce the risk for catheter-related bloodstream infection by approximately 50% in hospitalized patients who require short-term catheterization. Given the extent of the benefit and the small incremental cost, chlorhexidine gluconate should be considered as a replacement for povidone-iodine solution, particularly in patients at high risk for catheter-related bloodstream infection.

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