

Use of Vancomycin-Containing Lock or Flush Solutions for Prevention of Bloodstream Infection Associated with Central Venous Access Devices: A Meta-Analysis of Prospective, Randomized Trials

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Background. Prolonged exposure to central venous access devices carries significant risk of device-associated bloodstream infection (BSI), which is associated with morbidity, added health care costs, and attributable mortality. We aimed to determine the efficacy of vancomycin-heparin lock or flush solution in preventing BSI in patients being treated with long-term central venous intravascular devices (IVDs).

Methods. We collected data from January 1966 to January 2006 from multiple computerized databases and compiled reference lists of identified articles. We identified prospective, randomized controlled trials comparing a vancomycin-heparin lock or flush solution with heparin alone for prevention of BSI associated with long-term central venous IVDs. Using a standardized form, we abstracted data regarding study quality, patient characteristics, and incidence of BSI.

Results. Seven randomized, controlled trials involving a total of 463 patients being treated with IVDs met the inclusion criteria; 5 studies were conducted among patients with cancer, 1 among a critically ill neonatal population, and 1 among patients with cancer or who required parenteral nutrition. We could not detect publication bias. The summary risk ratio with a vancomycin heparin-lock solution for IVD-associated BSI was 0.49 (95% confidence interval [CI], 0.26–0.95; $P = .03$). Results of the test for heterogeneity were statistically significant; however, when a single study was removed from the analysis, heterogeneity was no longer present. Use of vancomycin as a true lock solution—instilling it for a defined period, rather than simply flushing it directly through the device—conferred a much greater benefit, with a risk ratio of 0.34 (95% CI, 0.12–0.98; $P = .04$). The 2 studies that performed prospective surveillance cultures to identify colonization or infection by vancomycin-resistant organisms did not find an increased risk.

Conclusions. Use of a vancomycin lock solution in high-risk patient populations being treated with long-term central IVDs reduces the risk of BSI. The use of an anti-infective lock solution warrants consideration for patients who require central access but who are at high risk of BSI, such as patients with malignancy or low-birthweight neonates.

Prolonged central venous access is essential for critically ill neonates requiring parenteral alimentation and for children and adults requiring intensive cancer chemotherapy, bone marrow or solid organ transplants, home antibiotic therapy, or lifelong hemodialysis or total parenteral nutrition [1, 2]. More than 5 million

US patients require prolonged central venous access each year [3, 4]. The intravascular devices (IVDs) available for long-term central access include cuffed and tunneled central venous catheters, subcutaneous ports, and peripherally inserted central venous catheters [3]. Although reliable, these devices are nonetheless associated with considerable risk of IVD-associated bloodstream infection (BSI) [3, 4]. Device-associated BSIs increase antibiotic exposure, length of hospital stay [5–8], health care costs [5, 6, 8], and mortality [5–7, 9].

For microorganisms to cause an infection associated with an IVD, they must first gain access to the extraluminal or intraluminal surface of the device, where they can adhere and become incorporated into a biofilm that

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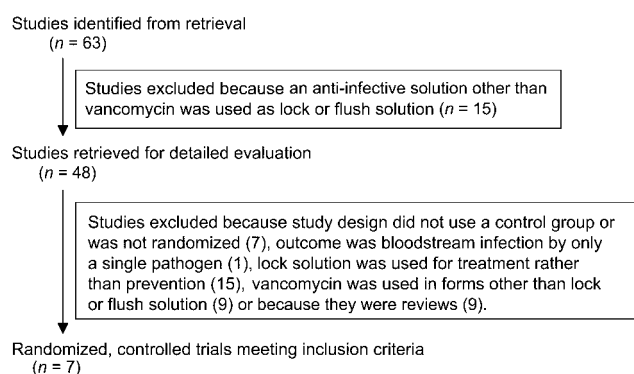


Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis.

allows sustained colonization and, ultimately, hematogenous dissemination [10]. Microorganisms gain access to an implanted IVD by 1 of 3 mechanisms, as follows: skin organisms invade the percutaneous tract extraluminally, probably facilitated by capillary action [11], at the time of catheter insertion or in the days following insertion; microorganisms contaminate the catheter hub (and lumen) when the device is inserted over a guidewire or is later manipulated during use [12]; or organisms are carried hematogenously to the implanted device from remote sources of local infection, such as a pneumonia.

In contrast to short-term IVDs, where the extraluminal route of infection predominates [13–15], most BSIs that occur in association with long-term devices are caused by intraluminal contaminants [16–18]. A promising approach to preventing these infections has involved instilling (i.e., locking) an anti-infective solution into the device lumen or lumens to prevent colonization of the intraluminal surface by suspended planktonic-phase contaminants [19–21]. Because the majority of BSIs associated with IVDs are caused by gram-positive organisms, particularly coagulase-negative staphylococci [22–25], vancomycin in combination with heparin has been the best studied prophylactic lock solution. We report a meta-analysis of prospective, randomized trials evaluating the efficacy of a lock or flush solution containing vancomycin and heparin (with or without an anti-infective agent for gram-negative organisms), compared with a heparin lock solution alone (control), for preventing BSI in patients being treated with long-term central venous access devices.

METHODS

Study selection. Medline, PubMed, Embase, Web of Science, and the Cochrane Library databases were searched for relevant publications from the date of each database's inception until 12 January 2006. No language restrictions were applied. The following keywords were used alone and in combination: antibiotic lock technique, lock solution, vancomycin lock, heparin

lock, flush solution, bacteremia, and bloodstream infection. Only randomized, clinical trials were included. A librarian at our institution assisted in the search to ensure that no relevant studies were missed. We also reviewed the reference lists of retrieved articles and of recent review articles. Studies in abstract form were sought by perusing proceedings and abstracts of the following annual scientific conferences: Interscience Conference on Antimicrobial Agents and Chemotherapy, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Society for Pediatric Research, and American Society of Hematology. Authorities in the field were also contacted to identify additional studies.

Inclusion criteria. To be included in the meta-analysis, a study needed to meet the following criteria; each study needed to (1) be a randomized trial comparing a vancomycin-heparin lock or flush solution (with or without a gram-negative anti-infective agent) with heparinized saline alone; (2) provide clear, microbiologically based definitions for BSI; and (3) include a report on the incidence of BSI with sufficient information to allow calculation of a relative risk. Studies that focused on lock solutions containing drugs other than vancomycin, that were not randomized, controlled trials, that used outcome measures other than BSI, that focused on treatment of rather than prevention of BSI in patients being treated with IVDs, and that used continuous infusions of vancomycin for prevention of device-related bacteremia were excluded.

Outcome measures. The primary outcome measure was BSI, which we defined as bacteremia or fungemia without another source in the presence of an IVD, with signs and symptoms consistent with systemic infection.

Data extraction. Using a standardized data form, we independently abstracted data regarding the size of the study sample, type of patient population, type of vascular device used, the lock or flush regimen, duration of device insertion, and incidence of BSI. We also evaluated the following methodologic components of each study: randomization procedure, blinding, and description of eligible participants. Disagreements among the investigators abstracting the data were resolved by discussion. The authors of studies that did not contain sufficient data were contacted for additional information. The QUORUM (quality of reporting of meta-analyses) checklist was followed for study selection, data abstraction, data synthesis, and reporting of results [26].

Statistical analysis. Pooled estimates of the risk ratio and 95% CI were obtained using the DerSimonian and Laird random effects model [27] and the Mantel-Haenszel fixed effects model [28]. Heterogeneity was assessed using the Cochran Q statistic and I^2 test, $[100\% \times (Q - df)/Q]$, where Q is Cochran's Q statistic and "df" is degrees of freedom [29]. Degrees of freedom are equal to $k - 1$, where k is the number of studies. Negative values of I^2 are put equal to 0%, so that I^2 values can

Table 1. Characteristics of trials fulfilling criteria for inclusion in the meta-analysis.

Study	Patient population	Vancomycin concentration and details of lock protocol	Type of IVD	Duration of IVD placement, mean or median days (total line days)		No. of episodes of BSI/ no. of catheters		Prospective surveillance cultures for detection of vancomycin-resistant bacteria colonization
				V-H group	Heparin group	V-H group	Heparin group	
[88]	Children with hematologic malignancy	25 µg/mL flush solution used whenever an IVD was used	TC CVC	228 (4792)	262 (6303)	3/24	8/29	No
[89]	Children with hematologic malignancy	25 µg/mL flush solution used whenever an IVD was used	TC CVC	137 (4378)	154 (4780)	10/32	10/31	No
[91]	Children with hematologic malignancy	25 µg/mL flush solution used whenever an IVD was used	TIP	350 (9814)	295 (10033)	2/30	3/34	No
[86]	Adults with cancer	25 µg/mL lock solution that was allowed to dwell for 60 min every 2 days	CVC	10 (600)	11 (627)	15/57	17/60	No
[90]	Children with hematologic malignancy	25 µg/mL lock solution used whenever an IVD was used	TC CVC	201 (8059)	200 (18045)	6/35	31/80	Yes ^a
[85]	Patients in the NNICU	25 µg/mL lock solution that was allowed to dwell for 20–60 min daily	PICCs	20 (840)	19 (860)	7/42	18/43	Yes
[87]	Children with cancer	25 µg/mL flush solution used whenever an IVD was used	TC CVC	205 (8011)	196 (8666)	18/39	26/44	No

NOTE. BSI, bloodstream infection; IVD, intravascular device; NNICU, neonatal intensive care unit; PICC, peripherally inserted central catheter; TC CVC, tunneled and cuffed central venous catheters; TIP, totally implanted ports; V-H, vancomycin and heparin.

^a Assessed in a later part of the study.

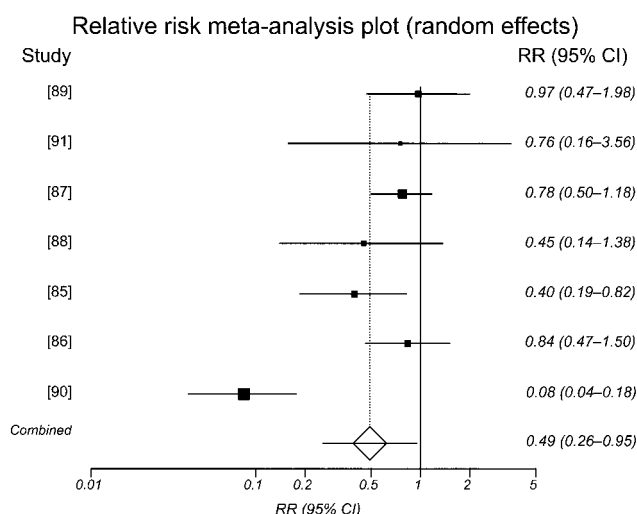


Figure 2. Analysis of studies comparing a vancomycin-containing lock or flush solution and heparin alone for prevention of bloodstream infection in patients with intravascular devices. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary risk ratio is 0.49 (95% CI, 0.26–0.95; $P = .03$), indicating a significant protective effect of a vancomycin-heparin lock or flush solution. RR, relative risk.

range from 0% to 100%. Zero percent indicates no observed heterogeneity; larger values indicate increasing heterogeneity. Subgroup analyses were used to explore the reasons for heterogeneity. Publication bias was assessed using a funnel plot and the Eggers statistical test [30, 31]. All statistical analyses were performed using Stats Direct software (StatsDirect).

RESULTS

Our search yielded 63 published reports (figure 1); 56 studies were excluded because they evaluated lock solutions other than vancomycin [32–46], did not have a control group [47–50], used a lock solution for treatment rather than prevention [45, 51–65], did not use a randomized, controlled study design [66–69], assessed the utility of a lock solution for prevention of BSI with only 1 type of organism [70], were reviews [19, 20, 56, 71–76], or used vancomycin in forms other than a lock or flush solution [66, 77–84].

Seven trials fulfilled inclusion criteria [85–91]. The characteristics of the included trials are shown in table 1. These studies encompassed 463 patients. Five trials exclusively studied patients with cancer [86–88, 90, 91]; 1 trial studied neonates [85]; and 1 trial studied patients with cancer as well as children requiring total parenteral nutrition [89]. Patient age ranged from neonates with very low birth weight to adults. However, most studies were of children. In every study, long-term IVDs were used. Two studies prospectively evaluated the effect of the lock solution on cutaneous or gastrointestinal colonization by

vancomycin-resistant microorganisms by serial surveillance cultures and selective vancomycin-containing media [85, 90].

Vancomycin was used in a concentration of 25 $\mu\text{g/mL}$ in all 7 studies. Five studies used vancomycin combined with heparin alone, 1 study used a vancomycin-amikacin-heparin solution [91], and 1 study had 2 treatment groups: recipients of vancomycin-heparin alone and recipients of a vancomycin-ciprofloxacin-heparin solution [90]. The vancomycin-ciprofloxacin-heparin solution arm was not included in the analysis. All studies used heparinized saline as the comparator.

Studies used either lock solutions or flush solutions (table 1). We considered solutions to be lock solutions if they were allowed to dwell in the lumen of the IVD for a prescribed period of time and if the device was not immediately used for parenteral infusion. Of the studies that used this criteria, 4 evaluated a vancomycin-heparin lock solution [85, 86, 88, 90], and the remainder evaluated a vancomycin-heparin flush solution. In 2 studies, after a specified time period, the lock solution was aspirated and discarded [85, 86]; in the remaining 5 studies [87–91], the solution was flushed into the bloodstream.

Of the 7 studies, 3 described IVD care procedures [85, 86, 89], and 5 reported details of the randomization procedure, which was adequate in each case [85, 86, 88, 90, 91]. Every study was a double-blinded trial.

The diagnostic criteria used for BSIs were as follows: bacteremia or fungemia documented during a febrile episode by at least 1 catheter-drawn or peripheral blood culture [86, 91]; bacteremia related to the catheter (defined as a 10-fold higher concentration of bacteria drawn through the IVD, compared with peripheral blood culture, positive results from a qualitative catheter-drawn blood culture [88, 90], or positive results of a peripheral blood culture with concordant colonization of the hub or tip [85]) and unrelated to the catheter (defined as positive results of qualitative peripheral and catheter-drawn blood cultures, a >10-fold difference in concentration between

Table 2. Sensitivity analysis to explore heterogeneity in studies of vancomycin-containing lock or flush solutions for prevention of bloodstream infection.

Study	Summary risk ratio (95% CI)	Test of heterogeneity
All studies	0.49 (0.25–0.95)	<.0001
All except [89]	0.43 (0.20–0.92)	<.0001
All except [87]	0.44 (0.19–1.01)	<.0001
All except [90]	0.72 (0.55–0.95)	.55
All except [88]	0.49 (0.21–1.03)	<.0001
All except [85]	0.51 (0.23–1.10)	<.0001
All except [86]	0.44 (0.20–0.98)	<.0001
All except [91]	0.47 (0.23–0.95)	<.0001

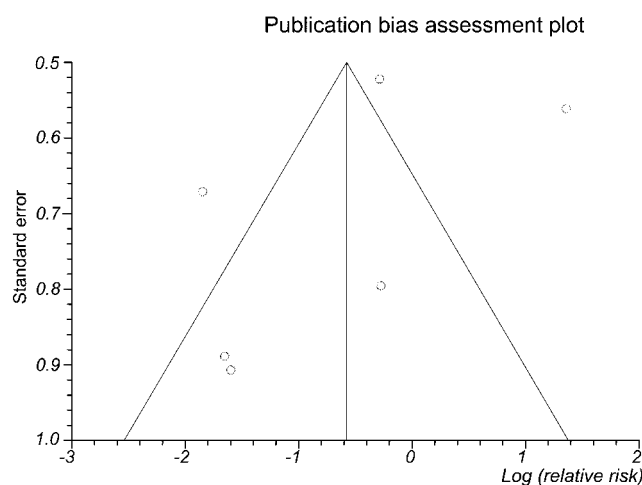


Figure 3. Funnel plot to assess publication bias. Each circle represents 1 study. Publication bias was not detected.

peripheral and catheter-drawn blood cultures, negative results of a catheter-drawn blood culture coupled with positive results of a peripheral blood culture [88, 90], or positive results of a percutaneous or catheter-drawn blood culture with no other source for the BSI [85, 87, 89]). The studies included used widely differing diagnostic criteria for IVD-related BSI, and some studies only evaluated infection caused by vancomycin-susceptible organisms or infection attributable to luminal colonization. Therefore, we did not combine the studies to assess IVD-related BSI as an outcome. The primary outcome measure in this meta-analysis was all BSIs.

All BSIs

The overall summary risk ratio using the random effects model was 0.49 (95% CI, 0.26–0.95; $P = .03$) (figure 2), indicating a significantly reduced risk of all BSIs for patients randomized to receive a vancomycin lock or flush solution. The test of heterogeneity was statistically significant ($P = .007$). To examine this heterogeneity and the effect of each study on the overall result, we tested the sensitivity of our results to the exclusion of each study (table 2). The results show that the study by Henrickson et al. [90] accounted for all of the heterogeneity. Exclusion of the study by Henrickson et al. [90], but not any of the other studies, removed the heterogeneity.

The I^2 test for heterogeneity had a value of 80%, indicating a large degree of heterogeneity. Results of tests for publication bias were not statistically significant. The funnel plot is shown in figure 3. The results using the fixed effects models were similar.

Subgroup Analyses

Effect of true lock solutions on BSIs. To determine whether prolonged exposure of the IVD lumen to vancomycin, as occurs

with a lock rather than a flush solution, might have greater efficacy in reducing the risk of BSI, we performed a subgroup analysis stratified by a lock or flush protocol. Four studies used a lock solution [85, 86, 88, 90], and 3 used a flush solution [87, 89, 91]. Studies using a lock solution had a summary risk ratio of 0.34 (95% CI, 0.12–0.98; $P = .04$) (figure 4), indicating a 64% statistically significant relative reduction, whereas the risk ratio for studies of flush solutions was 0.82 (95% CI, 0.58–1.17; $P = .27$), indicating a nonsignificant relative reduction of 18% (figure 5). The test for heterogeneity was statistically significant in the subgroup analysis, and these analyses were performed using random effects models.

Analyses stratified by type of population. Analyses were repeated, excluding the study by Garland et al. [85], because it was the only study in a population without cancer. The relative risk was 0.51 (95% CI, 0.23–1.10), indicating a 49% relative risk reduction with the use of a vancomycin lock or flush solution; however, the results were no longer statistically significant ($P = .10$).

Adverse effects of lock solutions containing vancomycin and heparin. Only 2 studies rigorously assessed for adverse reactions associated with the use of the lock solution [85, 88]. No adverse events were found in 1 study [88]. In another study [85], hypoglycemia resulting from interruption of parenteral alimentation occurred in 18 (41%) of 42 neonates with very low birth weight in the control group, compared with 8 (19%) of 42 neonates in the vancomycin-heparin lock solution group; all patients responded promptly to an infusion of glucose-con-

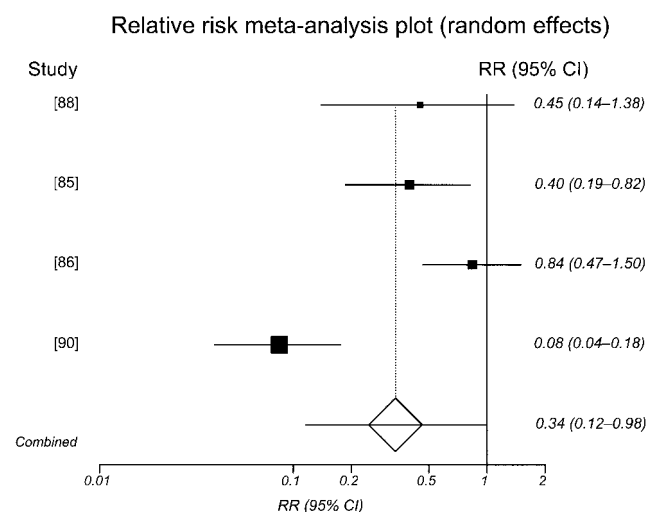


Figure 4. Analysis of studies comparing a vancomycin-containing lock solution and heparin alone for prevention of bloodstream infection in patients with intravascular devices. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary risk ratio is 0.34 (95% CI, 0.12–0.98; $P = .04$), indicating a significant protective effect of a vancomycin-heparin solution used in a lock protocol. RR, relative risk.

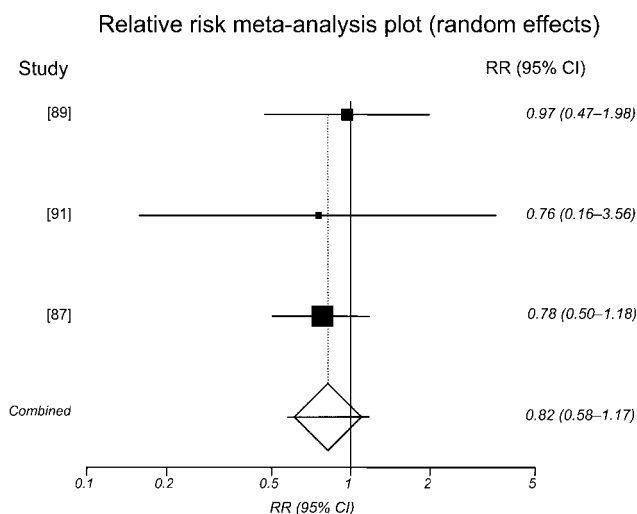


Figure 5. Analysis of studies comparing a vancomycin-containing flush solution and heparin alone for prevention of bloodstream infection in patients with intravascular devices. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary risk ratio is 0.82 (95% CI, 0.58–1.17; $P = .27$), suggesting a protective effect of a vancomycin-heparin solution used in a flush protocol; however, the results are not statistically significant. RR, relative risk.

taining fluid. Serum concentrations of vancomycin were measured in 2 studies [85, 88] and were uniformly found to be undetectable in the absence of concurrent intravenous vancomycin therapy.

Emergence of antibiotic-resistant organisms with use of lock solution containing vancomycin and heparin. None of the 7 studies encountered any device-related BSI or colonization of IVDs by vancomycin-resistant organisms. Of the 7 studies, 2 were prospectively evaluated for nosocomial colonization with vancomycin-resistant organisms by serial surveillance culture of skin or rectum specimens [85, 90]; vancomycin-resistant organisms were not detected in 1 of the 2 studies. In the study by Henrickson et al. [90], 1 patient had a culture of a rectal specimen that was positive for vancomycin-resistant enterococcus 4 months after beginning daily use of vancomycin-heparin lock solution.

DISCUSSION

Prevention of bloodstream infections in patients with IVDs is essential. The prophylactic use of systemic antibiotics at the time of IVD insertion or implantation has not proven to be effective in reducing the incidence of IVD-related BSI with long-term devices [92], and the practice is strongly discouraged in the 2002 Guidelines of the Hospital Infection Control Policy Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention [93]. Whereas studies of continuous intravenous infusion of vancomycin have shown reduced rates of coagulase-negative staphylococcal bacteremia in infants with

low birth weight [25, 83], this approach to prevention is also strongly discouraged in the HICPAC guideline because of the fear of promoting vancomycin resistance [93].

An anti-infective lock is a novel technique of local prophylaxis in which the anti-infective solution is instilled into the IVD lumen and allowed to dwell for a prescribed period of time (20–60 min or up to 6–24 h), after which it is removed or flushed into the patient's bloodstream. Most BSIs originating from long-term devices are intraluminally derived [16–18], especially those caused by coagulase-negative staphylococci. Vancomycin has been the anti-infective agent most extensively studied as a lock or flush solution for patients requiring long-term central access.

Our analysis of 7 prospective, randomized trials shows a ~50% reduction in the relative risk for BSI associated with the use of a vancomycin-heparin lock or flush solution (figure 2). Analysis of the 4 studies that used a true lock rather than a flush solution shows that when a vancomycin-heparin lock solution was used in a lock protocol, it conferred a 64% risk reduction (figure 4), probably because of the prolonged luminal contact time with the antibiotic.

A recent meta-analysis conducted by the Cochrane Network on the efficacy of vancomycin- or teicoplanin-containing flush solutions for the prevention of gram-positive central venous catheter-related BSI revealed a 65% relative risk reduction with the use of a flush solution (OR, 0.35; 95% CI, 0.16–0.77) [94]. However, the primary outcome was bacteremia caused by gram-positive organisms only, and the use of lock solutions was not assessed.

Concerns have been raised that this novel form of local antimicrobial prophylaxis will promote resistance. IVD colonization or BSI with vancomycin-resistant organisms was not encountered in any of the 7 trials, although the issue was addressed rigorously in only 2 trials [85, 90]. We believe that it is highly unlikely that microorganisms in a patient's microflora would develop resistance to vancomycin from the infinitesimal quantities of vancomycin used in a IVD lock or flush protocol (<25 μg), because it was not possible to detect vancomycin in patients' blood in any of the studies. Because most of the studies included in our analysis were undertaken in children, and the risk of acquiring infection with vancomycin-resistant enterococci may be different for children and adults, future studies should rigorously assess this concern. Moreover, surveillance for an increase in the institutional prevalences of antimicrobial resistant organisms should continue.

Because vancomycin-lock solutions clearly reduce the risk of BSIs associated with long-term IVDs, the 2002 HICPAC guideline considers their use to be acceptable, but only in individual cases in which the patient requires indefinite vascular access (e.g., patients with short bowel syndrome or patients who require maintenance hemodialysis) and continues to experience

Table 3. Randomized controlled trials of other anti-infective lock solutions for prevention of bloodstream infection (BSI).

Study	Patient population	Anti-infective lock solution	Diagnostic criteria for CRBSI	Anti-infective solution concentration and details of lock protocol	Type of IVD	Duration of IVD placement, mean or median days (total line days)		No. of IVDs associated with BSI/ no. of IVDs or patients studied		Relative risk (95% CI)
						Anti-infective solution group	Comparator group	Anti-infective solution group	Comparator group	
[38]	Patients undergoing hemodialysis	Gentamicin-citrate	Concordance between semiquantitative catheter segment and blood culture result	40 mg/mL gentamicin and 3.13% citrate in a 2:1 ratio; lock solution instilled after each dialysis	TC CVC	40 (3280)	35 (2643)	0/53	7/55	.07 (.007–.70)
[96]	Patients undergoing hemodialysis	Taurolidine-citrate	Primary BSI	1.35% taurolidine and 4% citrate lock solution instilled after each dialysis	TC CVC and nontunneled CVC	41 (1519)	48 (1885)	0/37	4/39	.13 (.01–1.29)
[34]	Patients undergoing hemodialysis	Gentamicin-heparin	Primary BSI	5 mg/mL gentamicin and 5000 IU/mL heparin flush solution used whenever an IVD was used	TC CVC	130 (3252)	103 (2470)	1/25	6/25	.16 (.02–.94)
[32]	Patients undergoing hemodialysis	Minocycline-EDTA	Catheter colonization and a positive peripheral blood culture result	3 mg/mL minocycline and 30 mg/mL EDTA flush solution instilled after each dialysis	Temporary hemodialysis catheter	89 (NR)	65 (NR)	0/30	1/30	...

NOTE. CRBSI, catheter-related BSI; IVD, intravascular device; TC CVC, tunneled and cuffed central venous catheters.

episodes of device-related BSI despite stringent adherence to preventive guidelines [93].

The next step should be to identify anti-infective lock solutions with broad-spectrum anti-infective activity against both multiresistant gram-positive and gram-negative bacteria, as well as fungi, but one that will not select for resistance. Novel agents that have shown promise in pilot studies include taurolidine [42], minocycline-EDTA [33], gentamicin-citrate solution [38], and US pharmacopeia-grade ethanol [95]. Only a few randomized trials of these novel agents have been conducted (table 3), but additional studies are underway.

Taurolidine is a derivative of aminosulfonamide-taurinamide, which has antimicrobial activity against a broad range of bacteria and fungi. Taurolidine has been studied in patients undergoing hemodialysis; in the only randomized trial published to date, Betjes et al. [96] reported 4 cases of IVD-related BSI in the heparin control group, compared with none in the taurolidine group (relative risk, 0.13; 95% CI, 0.01–1.29) (table 3).

EDTA is a potent calcium and iron chelator, that in addition to its anticoagulant effects, exhibits antistaphylococcal and anticandidal activity. In a randomized trial of the minocycline-EDTA solution in patients undergoing hemodialysis, Bleyer et al. [32] found reduced rates of colonization among patients with hemodialysis catheters; however, a major limitation to the study was that a considerable proportion of patients with catheters were lost to follow-up.

A double-blind, randomized study of 112 tunneled catheters in 83 patients comparing heparin with gentamicin-citrate (40 mg/mL of gentamicin and 3.13% citrate; ratio, 2:1) as catheter-lock solutions. Infection rates per 100 catheter-days were 0.03 cases in the gentamicin group versus 0.42 cases in the heparin group ($P = .003$) [38]. Another trial of gentamicin in combination with heparin (rather than citrate) has also been undertaken among patients requiring hemodialysis. A single IVD-related case of bacteremia occurred in the gentamicin lock solution group, compared with 10 cases of catheter-related BSI in 6 patients in the heparin control group (0.3 cases versus 4 cases of BSI per 1000 catheter-days; $P = .02$; table 3) [34].

We have found that a 25% ethanol lock solution has been completely effective in preventing recurrent catheter-related BSI in a 22-year-old woman with short-bowel syndrome requiring total parenteral nutrition (20 cases of BSI over 40 months vs. none over 60 months during use of the ethanol lock; 6.9 cases versus 0 cases per 1000 IVD-days; $P < .01$) [95]. We subsequently showed that prolonged exposure of commercial polyurethane and silicone central venous catheters to ethanol in concentrations as high as 70% does not have a detrimental effect on the mechanical properties of the catheters [97], and we are now conducting a double-blinded, randomized trial to evaluate the efficacy of a 50% ethanol lock solution instilled

for 1–3 h once daily for the prevention of BSI with long-term IVDs.

Needleless valve connectors have come into nearly universal use in the United States as part of a national movement to reduce exposure of health care workers to bloodborne viruses, such as HIV, hepatitis B virus, and hepatitis C virus, from sharps-associated injuries [98, 99]. However, there has long been a nagging concern that needleless systems may pose higher risks of IVD-related BSI. During the past decade, outbreaks of IVD-related BSI associated with needleless devices in both hospitals and home-care settings have been reported [100–104]. There is now mounting evidence of an ongoing, greatly increased incidence of nosocomial BSI in many US hospitals that derives from a vulnerability to nosocomial contamination of the commercial needleless valve connectors that are now universally used for long-term IVDs [100, 101]. The route of infection is likely contamination of the needleless valve connector during IVD use, followed by intraluminal movement of microorganisms into the bloodstream. Use of an anti-infective lock solution could prevent microorganisms from gaining entry into the bloodstream from contaminated needleless valve connector access points.

Our meta-analysis has several limitations. First, 3 studies used vancomycin in a flush protocol rather than as a true lock solution. Secondly, there was substantial heterogeneity among the studies, which we explored using sensitivity analyses and found that it was caused by a single study. Finally, publication bias is always a concern in meta-analyses, because negative-finding studies are less likely to be published; however, we undertook an exhaustive search to identify unpublished studies, and our analysis does not suggest publication bias (figure 2).

In conclusion, we found that vancomycin used in a scheduled lock protocol (figure 4) can substantially reduce the risk of bacteremia in patients with long-term IVDs. Consideration should be given to the use of a vancomycin lock for preventing bacteremia in high-risk, vulnerable patients. Randomized trials of the anti-infective lock technique using novel agents that are unlikely to select for resistance to systemic antibiotics are needed.

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