

A Vancomycin-Heparin Lock Solution for Prevention of Nosocomial Bloodstream Infection in Critically Ill Neonates With Peripherally Inserted Central Venous Catheters: A Prospective, Randomized Trial

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ABSTRACT. *Objective.* Critically ill neonates are at high risk for vascular catheter-related bloodstream infection (CRBSI), most often caused by coagulase-negative staphylococci. Most CRBSIs with long-term devices derive from intraluminal contaminants. The objective of this study was to ascertain the safety and the efficacy of a vancomycin-heparin lock solution for prevention of CRBSI.

Methods. A prospective, randomized double-blind trial was conducted during 2000–2001 at a community hospital level III NICU. Very low birth weight and other critically ill neonates with a newly placed peripherally inserted central venous catheter were randomized to have the catheter locked 2 or 3 times daily for 20 or 60 minutes with heparinized normal saline ($n = 43$) or heparinized saline that contained vancomycin 25 $\mu\text{g}/\text{mL}$ ($n = 42$). The origin of each nosocomial bloodstream infection (BSI) was studied by culturing skin, catheter hubs, and implanted catheter segments and blood cultures, demonstrating concordance by restriction-fragment DNA subtyping. Surveillance axillary and rectal cultures were performed to detect colonization by vancomycin-resistant organisms. The main outcome measures were (1) CRBSIs and (2) colonization or infection by vancomycin-resistant Gram-positive bacteria.

Results. Two (5%) of 42 infants in the vancomycin-lock group developed a CRBSI as compared with 13 (30%) of 43 in the control group (2.3 vs 17.8 per 1000 catheter days; relative risk: 0.13; 95% confidence interval: 0.01–0.57). No vancomycin-resistant enterococci or staphylococci were recovered from any cultures. Vancomycin could not be detected in the blood of infants who did not receive systemic vancomycin therapy. Twenty-six neonates (8 vancomycin-lock group, 18 control group) had at the end of a catheter-lock period asymptomatic hypoglycemia that resolved promptly when glucose-containing intravenous fluids were restarted.

Conclusions. Prophylactic use of a vancomycin-heparin lock solution markedly reduced the incidence of CRBSI in high-risk neonates with long-term central cath-

eters and did not promote vancomycin resistance but was associated with asymptomatic hypoglycemia. The use of an anti-infective lock solution for prevention of CRBSI with long-term intravascular devices has achieved proof of principle and warrants selective application in clinical practice. *Pediatrics* 2005;116:e198–e205. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2674; bacteremia, bloodstream infection, central venous catheter/access device, nosocomial infections, premature infants, sepsis, vancomycin.

ABBREVIATIONS. CRBSI, catheter-related bloodstream infection; CDC, Centers for Disease Control and Prevention; RR, relative risk; CI, confidence interval.

Very low birth weight and other critically ill neonates require prolonged vascular access, which is now most widely achieved in current practice with peripherally inserted central venous catheters.¹ Prolonged vascular access in high-risk neonates is associated with a high risk for catheter-related bloodstream infection (CRBSI),^{2–6} which increases antibiotic exposure, length of stay, hospital costs, and mortality.^{7–10} A bloodstream infection can occur during central venous therapy in as many as 20% to 30% of low birth weight neonates.^{3,5–8,10}

For microorganisms to cause CRBSI, they first must gain access to the extraluminal or intraluminal surfaces of the implanted device, where they can adhere and become incorporated into a biofilm^{11,12} that allows sustained colonization and, ultimately, hematogenous dissemination. Whereas most infections with short-term catheters derive from skin organisms that gain access extraluminally,^{13–16} contamination of the catheter hub and lumen seems to be the predominant mechanism of CRBSI with long-term central venous catheters, including peripherally inserted central venous catheters.^{6,7,12,17–20}

CRBSIs in hospitalized neonates are most frequently caused by coagulase-negative staphylococci.^{2–10,17,18} Whereas the prophylactic use of systemic antibiotics at the time of catheter insertion has not been shown to reduce the incidence of catheter-related infection^{21,22} and is strongly discouraged by the 2002 Guideline of the Hospital Infection Control Policy Advisory Committee of the Centers for Disease Control and Prevention (CDC),²³ the prophylactic use of a vancomycin-containing lock solution, instilled into the catheter lumen to eradicate intralumi-

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nal contaminants, has been shown to reduce the incidence of CRBSI in adults²⁴ and older children²⁵ with cuffed and tunneled central venous catheters. However, concerns have been raised that this novel form of local, extracorporeal, antimicrobial prophylaxis will promote resistance to vancomycin.²⁶ Unfortunately, none of the previous studies of anti-infective lock solutions prospectively examined its impact on colonization or infection by vancomycin-resistant organisms.

We report the results of a prospective, randomized trial conducted to ascertain rigorously the safety and the efficacy of periodically locking the peripherally inserted central venous catheters of high-risk neonates with a vancomycin-heparin solution for prevention of CRBSI and the impact of the antimicrobial-lock solution on nosocomial colonization or infection by vancomycin-resistant Gram-positive organisms.

METHODS

Study Design

The study was a prospective, randomized, double-blind, comparative trial conducted between May 2000 and May 2001 in the 50-bed, level III NICU in St Joseph Regional Medical Center of Milwaukee, Wisconsin, where peripherally inserted central venous catheters are used routinely for vascular access. The study protocol was approved by the institutional review board, and written, informed consent was obtained from each infant's parents or guardians.

Enrollment, Randomization, and Study Drug Administration

All neonates who were admitted to the unit and would require a catheter for at least 48 hours were eligible for the study. Catheters were inserted percutaneously by staff neonatologists using maximal sterile barriers, including a sterile mask, cap, gloves and gown, and a large sterile drape.^{6,23} Insertion sites were disinfected with 10% povidone-iodine (Aplicare Inc, Branford, CT), and catheters were dressed with a polyurethane film dressing (Bioclusive; Johnson and Johnson Medical, Arlington, TX). Catheter sites were cleansed and redressed on a weekly basis or as needed if the dressing became loose or the site wet. Intravenous tubing was changed every 3 days when used for hyperalimentation and every 24 hours when used for intralipid therapy. Needless access ports were not used during the trial. Catheter hubs were cleansed with alcohol whenever the hub was accessed.

After the principle investigator (J.S.G.) or the study nurse (C.P.A.) obtained parental consent but before catheter insertion, participating neonates were randomized by the unit pharmacist using a computer-generated block randomization sequence that was kept in a locked pharmacy cabinet. Neonates were randomized to 1 of 2 lock protocols: the catheter was locked twice daily with 0.4 mL of heparinized normal saline (10 IU/mL; control group) or heparinized saline that contained vancomycin (25 µg/mL). The locking volume ensured that the entire lumen of the catheter and extension tubing was filled with the lock solution. The vancomycin-heparin lock solution was prepared following methods described by Henrickson et al.²⁵ The solution was allowed to dwell for 20 minutes in neonates who were being fed primarily by parenteral hyperalimentation and for 60 minutes when enteral feeding exceeded 20 mL/kg/day. At the end of the dwell time, the study lock solution was withdrawn; the catheter was flushed with heparinized saline; and infusion of intravenous fluids, medications, or hyperalimentation admixture was resumed. Catheters were not locked with either study solution during days of systemic vancomycin therapy or when the catheter was used for continuous infusions of insulin or vasoactive drugs. Concomitant umbilical or arterial catheters were not locked. Only 1 catheter for each study patient was enrolled in the trial.

After the first 40 patients were enrolled, the frequency of locking catheters was increased from 2 to 3 times daily to assess

whether the number of daily locks affected CRBSI rates. However, because the hospital Infection Control Committee was concerned that the nosocomial bacteremia rate increased from 13.8 to 22.1 per 1000 catheter-days, in the next 21 neonates, whose catheters were locked 3 times daily, (relative risk [RR]: 1.6; 95% confidence interval [CI]: 0.73–3.09), the remaining 24 patients' catheters were locked twice daily.

Data Collection

Data were extracted prospectively from maternal and neonatal charts by 1 study nurse (C.P.A.) and included maternal and neonatal demographic information, 24-hour and 7-day neonatal acute physiology scores,²⁷ number of attempts needed to place the peripherally inserted catheter and its anatomic location, other medical devices used while the catheter was in situ, and the number of times each day the catheter was accessed to infuse medications or intravenous fluids. Each catheter lock was considered an access. Clinical and laboratory findings that were relevant to the diagnosis of infection were also extracted from each chart. Study neonates were followed by the study nurse until the catheter was removed.

Serum levels of vancomycin were measured (Dimension RXL; Dade, Wilmington, DE) on study days 7 and 14 in the first 73 patients before a study lock. Bedside whole-blood glucose concentrations were measured at the end of every 20-minute dwell and after every 20 and 40 minutes of a 60-minute dwell.

Surveillance rectal and axillary cultures were obtained with sterile cotton swabs premoistened with Stuart's media (Becton-Dickinson Microbiology Systems, Sparks, MD) at study entry and again at the time of catheter removal, inoculating the swab on brain-heart infusion agar that contained 6 µg/mL vancomycin. Gram-positive bacterial isolates that were recovered from catheter insertion sites, catheter cultures, or blood cultures were also tested for resistance to vancomycin. Microorganisms that showed growth on vancomycin-containing agar were considered resistant.²⁸

When infants showed signs suspicious for sepsis, as previously defined,⁶ 2 blood cultures were obtained: a 1-mL specimen drawn by percutaneous venipuncture and at least 0.5 mL drawn through the infant's catheter; the catheter hub was also cultured, using a premoistened sterile cotton swab.²⁹ Catheters were removed at the discretion of the attending neonatologist. At that time, a 1-cm × 1-cm area of skin surrounding the catheter, the catheter hub, and the distal 5 cm of the catheter each were cultured semiquantitatively, as previously described.²⁹

Microbiologic Methods

Standard laboratory methods were used to identify microorganisms that were recovered from cultures³⁰; all isolates of staphylococci and enterococci were tested for susceptibility to vancomycin, both by microtiter plate (Vitek; BioMerieux, Marcy, France) and by testing for growth on vancomycin-containing agar (6 µg/mL).²⁸ Strains of coagulase-negative staphylococci that were isolated from the blood, skin, catheter segments, or hubs of patients with catheter-associated bacteremia were subtyped by restriction-fragment polymorphism on pulsed-field gel electrophoresis,³¹ using an automated computerized system (Gel Doc 2000; Bio-Rad Laboratories, Hercules, CA) and CDC criteria³² for determining relatedness of isolates.

Definitions of Infection

Definite CRBSI

In an infant with signs of sepsis,⁶ a definite CRBSI was defined by a positive peripheral blood culture with concordant colonization of the catheter hub or catheter tip; when coagulase-negative staphylococci were isolated, clonal concordance was confirmed by restriction-fragment DNA subtyping. No other plausible source for the BSI was identifiable clinically or microbiologically, and the neonate was treated with at least 7 days of systemic antibiotic therapy.

Probable CRBSI

In an infant with signs of sepsis,⁶ a probable CRBSI was defined by either (1) a positive peripheral blood culture for coagulase-negative staphylococci, with concordant colonization of the cath-

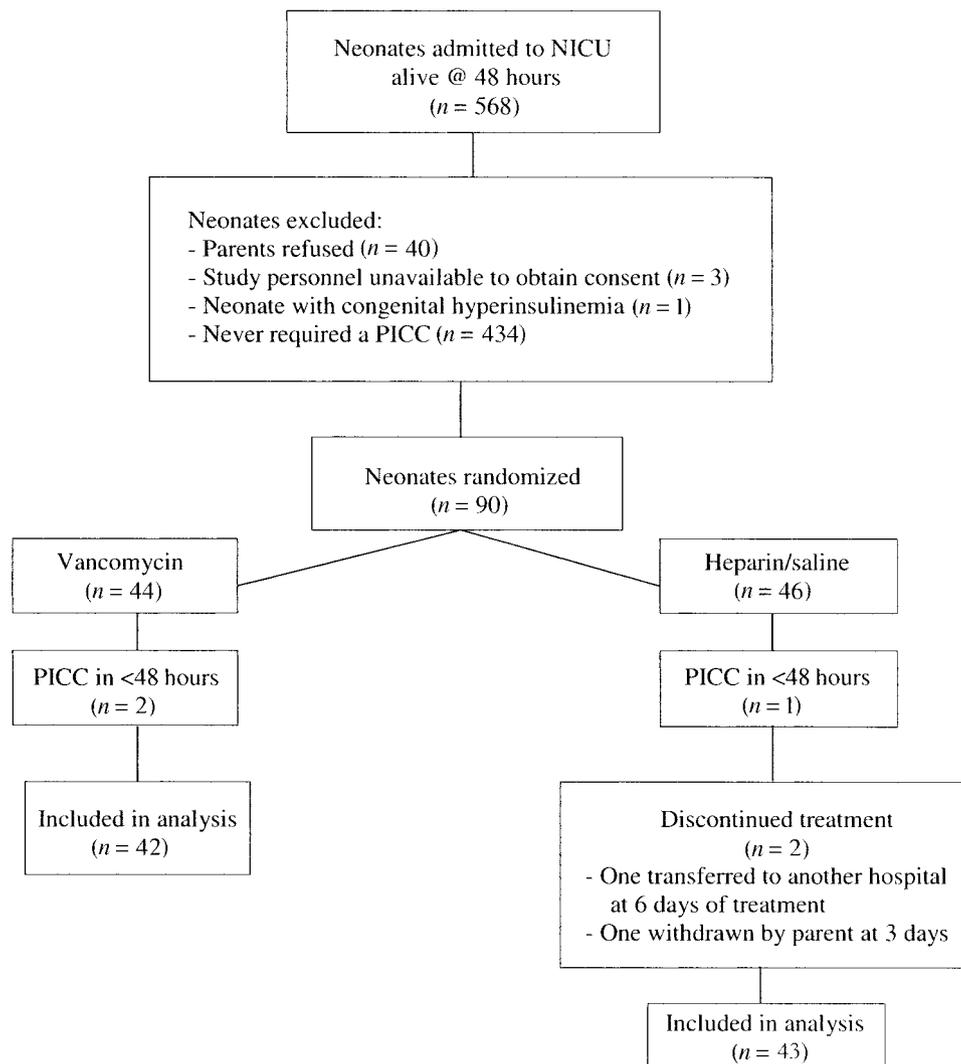


Fig 1. Flow diagram of neonates who were screened, enrolled, and randomly assigned to have their catheter locked with vancomycin or heparinized saline (controls). Reasons for exclusion and number of patients whose participation in the trial was discontinued are provided.

eter hub or tip, but DNA subtyping was not done or (2) a blood culture through the catheter was positive (peripheral culture sterile or not done) for the same organism recovered from the catheter hub or tip, with clonal concordance confirmed by DNA subtyping when the blood culture grew coagulase-negative staphylococci. In either case, no other plausible source for the BSI was found and the neonate was treated with at least 7 days of systemic antibiotic therapy.

BSI Without a Source

In an infant with signs of sepsis,⁶ a BSI without a source was defined by a positive peripheral or line blood culture and no other identifiable primary site of infection. Neonates were treated with at least 7 days of systemic antibiotic therapy. Cultures of the catheter were negative or, when positive, showed colonization with a strain or strains different from those recovered from the blood culture.

Outcome Measures and Statistical Analyses

Primary outcome measures included definite, probable, and definite plus probable CRBSIs and nosocomial colonization by vancomycin-resistant Gram-positive bacteria during the study and other adverse effects potentially ascribable to the catheter-lock regimen. Secondary outcome variables included BSI without a source and all nosocomial BSIs.

The trial was designed as a pilot with limited funding for 80 to

90 neonates; as such, it had 80% power to detect an 80% reduction in the combined rate of definite plus probable CRBSIs, from a projected baseline rate of 30 per 100 catheters to 5 per 100 catheters, with a 2-sided significance level of .05.

All outcome measures were analyzed by intention-to-treat, including all patients who had a catheter, were randomized, and received at least 1 dose of study lock solution. All analyses were performed by investigators who were blinded to group assignment. For preserving statistical independence, neonates with a CRBSI and an episode of BSI without a source during the trial were classified as having the primary outcome: CRBSI. The incidence (per 100 catheters) and incidence density (per 1000 catheter-days) of definite, probable, and definite plus probable CRBSI, BSIs without a source, and all nosocomial BSIs were calculated and compared by RR ratios and 2-sided 95% CIs. Data were analyzed by Statistical Analysis System 6.1 for the personal computer (SAS Institute, Cary, NC) or STATA Statistical Software: Release 7.0 (STATA Corp, College Station, TX). Differences in continuous variables between the 2 treatment groups were compared by unpaired *t* test or Wilcoxon rank-sum test; dichotomous variables were compared by Fisher exact test. Differences in primary outcomes were also compared using Mantel-Haenszel-Cochrane analyses. The proportion of catheters in each group that did not cause CRBSI as a function of time in place were compared using a log-rank test on the Kaplan-Meier estimates. In all comparisons, *P* < .05 in a 2-sided test was considered significant.

TABLE 1. Characteristics of the 2 Catheter-Lock Groups

	Heparin (n = 43)	Vancomycin and Heparin (n = 420)	P
Male, n (%)	28 (65)	23 (55)	.33
White, n (%)	20 (47)	22 (52)	.77
Inborn, n (%)	41 (95)	39 (93)	.68
Gestational age, wk, mean ± SD	28.3 ± 3.5	27.5 ± 3.8	.36
Birth weight, g, mean ± SD	1296 ± 735	1055 ± 718	.12
SNAP first day of life, mean ± SD	13.2 ± 6.2	12.7 ± 6.6	.70
Location of catheter, n (%)			
Arm	36 (84)	33 (79)	.26
Other	7 (16)	9 (21)	
First PICC placed, n (%)	41 (98)	38 (88)	.20
Insertion attempts, d, mean ± SD	2.3 ± 1.7	2.4 ± 2.2	.78
Duration catheter in place, d, mean ± SD	19.6 ± 12.3	20.3 ± 11.4	.78
While catheter in situ			
Umbilical catheter, n (%)	12 (28)	12 (29)	.95
Mechanical ventilation, n (%)	28 (65)	28 (67)	.88
Catheter entries per day, n, mean ± SD	5.7 ± 1.7	5.6 ± 2.0	.71
Hyperalimentation days, mean ± SD	18.1 ± 11.6	17.9 ± 10.6	.91
Lipid therapy days, mean ± SD	18.1 ± 11.6	17.4 ± 11.0	.76

SNAP indicates Score for Acute Neonatal Physiology; PICC, peripherally inserted central catheter.

TABLE 2. Nosocomial Bloodstream Infections in the Catheter-Lock Groups

N (%)	Heparin (n = 43)	Vancomycin and Heparin (n = 42)	RR (95% CI)	P
CCRBSI				
Definite	8 (19)	0	0	.006
Probable	5 (11)	2 (5)	0.41 (0.08–2.00)	.43
Total	13 (30)	2 (5)	0.16 (0.04–0.66)	.002
BSI without a source	5 (12)	5 (12)	1.02 (0.32–3.28)	.97
All BSIs	18 (42)	7 (17)	0.40 (0.19–0.85)	.01

RESULTS

Patient Population

As shown in Fig 1, during the study period (May 2000–May 2001), 85 of 134 neonates who had percutaneously placed central catheters and were potentially eligible for the trial were enrolled and randomized, 43 to the control group and 42 to the vancomycin-lock group. Neonates in the 2 treatment groups were similar with respect to baseline demographic characteristics, severity-of-illness scores, location and ease of catheter insertion, mean number of catheter entries per day, and the duration of catheterization, ~20 days in each group (Table 1).

Efficacy

CRBSIs

Definite CRBSI occurred in 8 (18.6%) of 43 neonates in the control group and none of 42 in the vancomycin-heparin-lock group ($P = .006$; Table 2). There were 13 total (definite and probable) CRBSIs in the control group and 2 in the vancomycin-lock group (RR: 0.16; 95% CI: 0.04–0.66; $P = .002$). Incidence density of all CRBSIs during the study was markedly reduced in neonates who were randomized to have their catheters locked with vancomycin and heparin (17.8 vs 2.3 per 1000 catheter-days; RR: 0.13; 95% CI: 0.01–0.57; $P = .004$), whether the lock solution dwelled for 20 minutes (16.1 vs 3.1 per 1000 catheter-days; RR: 0.19; 95% CI: 0.004–1.5; $P = .10$) or 60 minutes (30.7 vs 3.3 per 1000 catheter-days; RR: 0.11; 95% CI: 0.002–0.83; $P = .01$). Comparable protection was provided by vancomycin catheter locks

twice daily (14.1 vs 3.1 per 1000 catheter-days; RR: 0.22; 95% CI: 0.023–1.05; $P = .04$) as compared with 3 times per day (29.4 vs 0 per 1000 catheter-days; $P = .02$). Most episodes of definite (7 of 8) and probable (7 of 7) CRBSIs were caused by coagulase-negative staphylococci; a single episode was caused by *Candida albicans*. Catheters were removed at the time of a definite or probable catheter infection in 11 of 15 neonates who were infected by coagulase-negative staphylococci. None of the 14 neonates with coagulase-negative staphylococcal bacteremia died from the CRBSI, and other organ systems were not affected after the CRBSI. The Kaplan-Meier estimates of the cumulative likelihood of freedom from CRBSI at each day of catheter placement in each group show that the vancomycin-heparin lock protocol conferred a high level of protection (Fig 2).

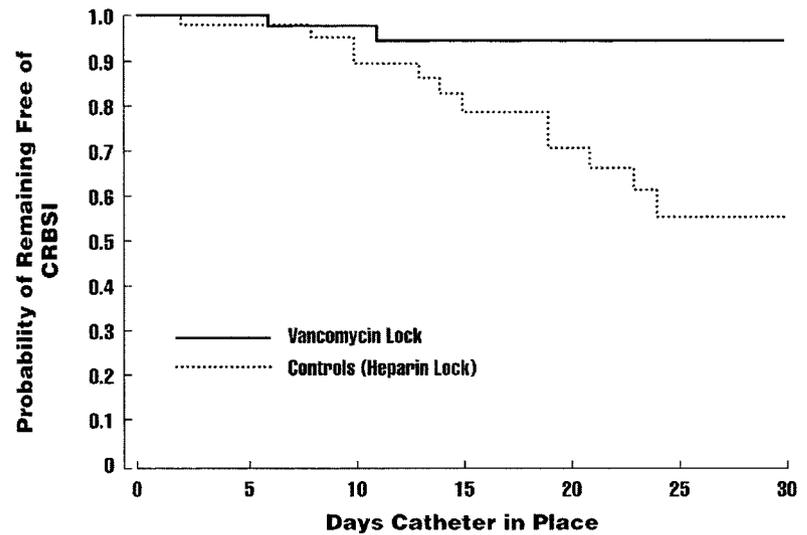
BSIs Without a Source

There was no significant difference between the 2 treatment groups in the incidence of BSI without a source (11.9% vs 11.6%; RR: 1.02; 95% CI: 0.32–3.3; $P = .97$; Table 2), and there were no differences in the profile of microorganisms that caused BSI without a source; 6 (3 in each study group) of the 10 cases were caused by coagulase-negative staphylococci, and 1 each was caused by *Enterococcus faecalis*, *Candida lusitanae* (vancomycin lock solution), *Escherichia coli*, and *Staphylococcus aureus* (control lock solution).

All Nosocomial BSIs

The overall incidence of nosocomial BSI, including all CRBSIs and BSIs without a source, was signifi-

Fig 2. Kaplan-Meier estimates of the cumulative likelihood of freedom from CRBSI in the 2 treatment groups. The difference between the 2 groups is highly significant ($P = .005$ by log-rank test).



Catheters remaining:							
Vancomycin	42	40	32	26	18	11	8
Control	43	38	29	21	15	9	7

TABLE 3. Adverse Effects in the 2 Catheter-Lock Groups

	Heparin ($n = 43$)	Vancomycin and Heparin ($n = 42$)
Detectable blood vancomycin level ($>2 \mu\text{g/mL}$) in infants not receiving systemic vancomycin therapy, n	0	1*
Colonization by vancomycin-resistant Gram-positive bacteria, n	0	0
MIC of Gram-positive isolate from skin, catheter or blood $>2 \mu\text{g/mL}$, n	0	0
Hypoglycemia ($<40 \text{ mg/dL}$), documented at least once, n (%)	18 (41)	8 (19)

MIC indicates minimum inhibitory concentration of 100% of all isolates.

* The infant had been receiving intravenous vancomycin therapy 24 hours before the specimen was obtained.

cantly lower in neonates in the vancomycin-lock group (41.9% vs 16.7%; RR: 0.40; 95% CI: 0.19–0.85; $P = .01$); the incidence density was commensurately lower as well (24.9 vs 8.2 per 1000 catheter-days; RR: 0.33; 95% CI: 0.12–0.80; $P = .004$).

Safety and Tolerance

Only 1 neonate in the vancomycin-lock group had a detectable level of vancomycin in serum (4.3 $\mu\text{g/mL}$); the specimen had been drawn 24 hours after intravenous vancomycin had been discontinued. No vancomycin-resistant microorganisms were detected in any skin or rectal surveillance cultures in either group, either at study entry or at the time the study catheter was removed, and no isolate of Gram-positive bacteria recovered from skin, catheter, or blood cultures showed a minimal inhibitory concentration $>2 \mu\text{g/mL}$ (Table 3). Mean days of systemic vancomycin therapy was similar for heparin and vancomycin-lock-treated neonates (6.0 ± 6.8 vs 5.4 ± 7.2 days; $P = .56$).

Hypoglycemia, defined as a bedside whole-blood glucose concentration $\leq 40 \text{ mg/dL}$, occurred during a catheter dwell of lock solution in 26 (31%) of the 85

participants, 18 (41%) of the infants in the control group as contrasted with 8 (19%) in the vancomycin-lock group ($P = .03$; Table 3). Median number of dwells in which the blood glucose was $\leq 40 \text{ mg/dL}$ was 2 (range: 1–8) in the 26 neonates with hypoglycemia. No neonates were clinically symptomatic when hypoglycemic. Blood glucose concentrations rose promptly to $\geq 50 \text{ mg/dL}$ after infusion of glucose-containing fluid was resumed. Hypoglycemia followed 48 (3.6%) of 1322 control dwells and 15 (1.2%) of 1252 vancomycin-heparin dwells. Nine neonates (9 of 2574 study dwells) had a bedside blood glucose $\leq 30 \text{ mg/dL}$ at the end of a dwell. All bedside glucose concentrations $\leq 40 \text{ mg/dL}$ occurred at the end of a 20-minute dwell or during the first 20 minutes of a 60-minute dwell. Seventeen of 26 neonates with hypoglycemia (51 dwells) were receiving $<10 \text{ mL/kg/day}$ enteral feedings. Hypoglycemia occurred at the end of a dwell just 6 times in infants who received at least 30 mL/kg/day enteral feeds. Only 1 neonate with a definite or probable infection was hypoglycemic at the end of a dwell on the day the CRBSI was diagnosed.

TABLE 4. Meta-analysis of Prospective, Randomized Trials of a Vancomycin and Heparin Catheter-Lock Solution for Prevention of CRBSI

Study	No. of CRBSIs/No. of Catheters Studied				<i>P</i>
	Patient Population	Heparin	Vancomycin and Heparin	RR (95% CI)	
Schwartz et al ⁴²	Children	6/29	1/24	0.20 (0.03–1.56)	.10
Rackoff et al ⁴³	Children	3/31	12/32	3.88 (1.21–12.42)	.02
Daghistani et al ⁴⁴	Children	3/34	2/30	0.76 (0.14–4.22)	.99
Carratala et al ²⁴	Adults	4/57	0/60	0.0	.05
Henrickson et al ²⁵	Children	12/80	2/73	0.18 (0.04–0.79)	.01
Present trial	Neonates	13/43	2/42	0.16 (0.04–0.66)	.002
All studies (pooled)		41/274	19/261	0.49 (0.29–0.82)	.006

DISCUSSION

Most low birth weight and other critically ill neonates require stable and prolonged venous access.¹ This is now achieved in neonatal units around the world with central venous catheters, which, unfortunately, have been associated with very high rates of CRBSI.^{2–6,33,34} Whereas it is widely believed that peripherally inserted central catheters are associated with a lower risk of CRBSI than central catheters that are inserted percutaneously in a subclavian, internal jugular, or femoral vein, recent studies have shown that peripherally inserted central catheters that are used in hospitalized patients, including in high-risk neonates, have comparable rates of CRBSI in very low birth weight neonates in the range of 10 to 30 per 1000 catheter-days.^{5,6,8,10,33–35} This trial and an earlier study in our patient population⁶ reaffirm that peripherally inserted central venous catheters in critically ill neonates pose substantial risks for complicating BSI, reaffirming the need for more effective strategies for prevention.

Studies of continuous infusion of vancomycin in low birth weight infants have shown greatly reduced rates of nosocomial bacteremia caused by coagulase-negative staphylococci^{8,36}; however, this approach to prevention produces prolonged low levels of vancomycin in blood and tissue, a milieu conducive to the emergence of vancomycin resistance. The antibiotic lock is a novel form of local prophylaxis in which an antibiotic solution is instilled into the catheter lumen and allowed to dwell for a proscribed period, after which it is removed. The success of continuous vancomycin infusions in prevention of catheter-related bacteremia,^{8,36} as well as uncontrolled studies that suggest that antibiotic lock solutions may be beneficial therapeutically in established CRBSIs with long-term devices,^{37,38} suggests that antibiotic lock solutions may well be effective for prevention of catheter-related bacteremias associated with long-term central devices, such as peripherally inserted central catheters, cuffed and tunneled central venous catheters, and subcutaneous central ports.

In this double-blind, randomized trial, locking neonates' peripherally inserted central catheters with a vancomycin-heparin solution for only 20 or 60 minutes twice daily markedly reduced the incidence of CRBSI (Table 2, Fig 1) and was not associated with colonization or infection by vancomycin-resistant organisms (Table 3). Locking twice daily provided as

much protection as 3 times a day. Most impressive, the overall incidence of nosocomial BSIs was greatly reduced (RR: 0.30; *P* = .01). Although vancomycin is not rapidly bactericidal for staphylococci, we hypothesize that its efficacy as a catheter lock solution may well derive from preventing adherence of planktonic-phase microorganisms to the wall of the catheter and forming a biofilm.

The only adverse effect of vancomycin-lock prophylaxis that was encountered in the trial was transient asymptomatic hypoglycemia. Most of these neonates (17 of 26) were receiving <10 mL/kg enteral feedings. We did not record intravenous dextrose concentration at the time of hypoglycemia, but in most cases, it was >12.5% because central catheters are routinely placed so that concentrated hyperalimentation solutions can be infused after umbilical catheter removal. Since completing the trial, we now use the vancomycin lock routinely in all of our critically ill neonates with long-term central venous catheters. Hypoglycemia has been obviated by reducing the dwell time to 10 minutes when the infant is receiving <30 mL/kg/day enteral feeding. Since adopting this protocol for vancomycin-lock prophylaxis, the incidence of nosocomial Gram-positive bacteremia has declined 41% and use of intravenous vancomycin, 60%, in a recent time-sequence study in 2 of our level III NICUs.³⁹

The overall rate of CRBSI (definite or probable) was greater than that reported in a previous trial⁶ done in our nursery. The number of times that catheters were accessed during the trial in control neonates was slightly greater than during the previous trial (5.7 ± 1.7 vs 4.5 ± 0.1), perhaps explaining the increased overall rate of CRBSI in control subjects noted in this trial compared with our previous work. However, in our previous trial, neonates weighed more and were older than those in the present trial. Others have reported similar rates or incidence densities of bloodstream infections among low birth weight neonates with central venous catheters.^{3,5,10,40,41} Even if the overall CRBSI rate had been 20% in control subjects, risk for any CRBSI still would have been less in vancomycin-lock neonates (*P* = .049).

Including the study we report, there now have been 6 prospective, randomized trials of a vancomycin-lock solution for the prevention of bacteremia with long-term intravascular devices (Table 4).^{24,25,42–44} Catheters or catheter hubs were not rou-

tinely cultured in the previous trials, and molecular subtyping to confirm the origin of each CRBSI also was not done. The 2 largest and best controlled earlier trials^{24,25} and our study found unequivocal benefit for prevention of CRBSI. A recent study in neonates did not show benefit⁴⁵; however, in this trial, a vancomycin solution was flushed directly through the catheter into the infant's bloodstream and not allowed to dwell for a proscribed length of time. Finally, our study also assessed prospectively the impact of a vancomycin-heparin lock solution on colonization or infection by vancomycin-resistant organisms, and none was detected.

Our trial and the pooled results of all 6 trials to date (pooled RR: 0.49; 95% CI: 0.29–0.82; $P = .006$; Table 4) can be regarded as a proof of principle: vancomycin-lock protocols can substantially reduce the risk for device-related BSI with long-term intravascular devices and are unlikely to select for nosocomial colonization or infection by vancomycin-resistant organisms. It would intuitively seem unlikely that microorganisms in a patient's microflora would develop resistance to vancomycin from the minute quantities used in a catheter-lock protocol (~10 μg), because it is not possible to detect vancomycin in patients' blood (Table 3).²⁵ Because vancomycin-lock solutions clearly reduce the risk of BSIs associated with long-term intravascular devices, the 2002 CDC Hospital Infection Control Policy Advisory Committee Guideline considers their use as acceptable in individual cases in which the patient requires indefinite vascular access (eg, short-bowel syndrome or maintenance hemodialysis) but continues to experience device-related BSIs despite stringent adherence to preventive guidelines.²³ Our trial provides strong scientific underpinning for this recommendation.

A vancomycin-heparin lock solution is likely to be effective only in preventing BSIs that are caused by vancomycin-susceptible Gram-positive bacteria. Prevention of Gram-negative CRBSIs would require addition of a second anti-infective to the lock solution, such as a fluoroquinolone.²⁵ However, Gram-positive organisms were responsible for 73% of late-onset BSIs in a recent survey of the National Institute of Childhood Diseases Network of Nurseries.¹⁰ In a previous randomized trial in our study population,⁶ 70% of all primary BSIs and 94% of all colonized catheters grew Gram-positive organisms that all were susceptible to vancomycin.

We believe that the next step should be to identify and clinically assess anti-infective lock solutions with broad-spectrum anti-infective activity, against both multiresistant Gram-positive and Gram-negative bacteria and fungi, but which will not select for resistance.⁴⁶ Limited studies to date suggest that the novel combination of minocycline and ethylenediaminetetra-acetic acid,^{47,48} gentamicin and citrate,⁴⁹ taurolidine,^{50,51} and USP grade ethanol^{52,53} each hold promise.

New infection-control strategies should always be assessed clinically, whenever possible, by prospective, randomized, adequately powered clinical trials, ideally double-blinded trials. The vast majority of studies of novel, technology-based approaches for

prevention of intravascular device-related infection in recent years have been done in adults.⁴⁶ More studies need to be done in children and neonates.

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