

# A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: A multi-center, controlled, randomized trial\*

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**Background and Purpose:** Catheter-related bloodstream infection is the greatest threat to the safety of patients on hemodialysis. Catheter lock solutions containing heparin have been linked to an increased risk of hemorrhage and thrombocytopenia.

**Objectives:** To ascertain the safety and efficacy for prevention of catheter-related bloodstream infection and catheter loss from patency failure of a novel catheter lock solution with antimicrobial and antithrombotic activity containing 0.24 M (7.0%) sodium citrate, 0.15% methylene blue, 0.15% methylparaben, and 0.015% propylparaben (C-MB-P), compared with heparin.

**Design:** Multicenter, prospective, randomized, open-label trial with patients studied for up to 6 months. An independent clinical evaluation committee assessing trial outcomes was blinded to patients' treatment assignments.

**Setting:** Twenty-five outpatient hemodialysis units.

**Patients:** Patients with end-stage renal disease receiving maintenance hemodialysis through a percutaneous cuffed and tunneled internal jugular hemodialysis catheters.

**Interventions:** Participants' catheters were locked between hemodialysis sessions with the C-MB-P lock solution or sterile saline containing 5000 units of unfractionated heparin (control).

**Measurements and Main Results:** We recorded and evaluated catheter-related bloodstream infections, catheter loss attributable to luminal thrombosis, and adverse events. A total of 407 patients participated in the trial (49,565 catheter days), 201 in the C-MB-P group and 206 in the heparin group. Patients in the two lock solution groups were comparable for risk factors predisposing to catheter-related bloodstream infection. Catheters locked with C-MB-P were significantly less likely to cause catheter-related bloodstream infection (0.24 vs. 0.82 per 1000 catheter days; relative risk, 0.29; 95% confidence interval, 0.12–0.70;  $p = .005$ ) and were less likely to be lost because of patency failure (0 vs. 4; log rank,  $p = .04$ ).

**Conclusions:** The novel C-MB-P lock solution is well tolerated, significantly reduces the risk of catheter-related bloodstream infection, and provides protection comparable to heparin against patency failure. (Crit Care Med 2011; 39:613–620)

**KEY WORDS:** antimicrobial; antithrombotic; lock solution; hemodialysis; bloodstream infection; catheters; central venous catheter

Approximately 360,000 U.S. patients with end-stage renal disease receive maintenance hemodialysis, and approximately 25%, 90,000 patients, receive maintenance through catheters (1–4). Loss of catheter patency because of thrombosis, an ever-present threat, is a common reason that a catheter needs to be replaced, and hemodi-

alysis catheters are routinely locked with an anticoagulant solution, unfractionated heparin, between dialysis sessions in most North American centers (5). This practice has been associated with an increased risk of hemorrhage (6, 7) and heparin-induced thrombocytopenia (8, 9). Despite prophylactic use of a heparin-containing lock solution, declining catheter blood flow from

intraluminal thrombus underlies the necessity to instill a thrombolytic such as tissue plasminogen activator into the catheter lumens of more than half of hemodialysis catheters in an effort to restore patency (5).

The greatest threat to the safety of patients dialyzed through catheters is catheter-related bloodstream infection (CRBSI); rates in recent prospective studies have ranged from two to five cases per 1000 catheter days (3, 10–13). CRBSI also commonly results in loss of the catheter and is associated with significant morbidity, including septic shock and a greatly increased risk for infective endocarditis and has an attributable mortality of at least 10% (3, 14, 15). It has been estimated that between 67,500 and 150,000 U.S. dialysis patients acquire a CRBSI each year (3).

For microorganisms to cause CRBSI, they must first gain access to the extraluminal or intraluminal surface of the implanted device, where they can adhere

**\*See also p. 875.**

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Coinvestigators participating in this study are listed in the Appendix.

Dr. Ash is the founder and reports ownership of Ash

Access Technology. Dr. Ash has stock ownership and options in Ash Access Technology and received patents from Ash Access Technology related to this product. Mr. Winger is employed by Ash Access Technology and reports ownership and stock options. Dr. Lavin is employed by Averion International. Averion International was compensated by Ash Access Technology for clinical monitoring, statistical analysis, and clinical event committee support for this study. Dr. Maki has not disclosed any potential conflicts of interest.

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and become incorporated into a biofilm that allows sustained colonization and, ultimately, hematogenous dissemination (16). Most bloodstream infections (BSIs) originating from permanent cuffed and tunneled central venous catheters are caused by intraluminal contaminants (17, 18). A promising approach to prevention of these infections involves instilling—locking—an anti-infective solution into each catheter lumen when not in use to prevent colonization of the intraluminal surface by planktonic-phase microorganisms that have gained access and can form a biofilm on the inner wall of the catheter. A wide variety of anti-infective lock solutions have been studied in randomized trials for prevention of CRBSI with hemodialysis catheters, and most have shown benefit (10–13).

We report a multicenter, randomized, controlled trial of a novel catheter lock solution containing sodium citrate, methylene blue, and parabens, which has both antimicrobial and antithrombotic activity, to ascertain its safety and efficacy for prevention of CRBSI and catheter loss from patency failure compared with heparin.

## METHODS

### The Novel Lock Solution

The new lock solution studied in this trial (Zuragen; Ash Access Technology, Lafayette, IN) is a deep blue, aqueous solution containing 0.24 M (7.0%) sodium citrate, 0.05% methylene blue, 0.15% methylparaben, and 0.015% propylparaben (C-MB-P). The solution has been shown to have rapid bactericidal activity *in vitro* against clinical isolates of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans* (19) and has shown bactericidal activity against *S. aureus* biofilms (20).

### Study Design and Setting

The AZEPTIC trial was a multicenter, prospective, randomized, open-label, parallel-group study of two lock solutions for prevention of CRBSI and loss of catheter patency from thrombosis conducted in 25 outpatient hemodialysis units in the United States. Participants remained in the trial for up to 6 months, with a six month Extension Phase for safety monitoring of C-MB-P patients only. The study protocol was approved by the Food and Drug Administration under an Investigational Device Exemption and by Institutional Review Boards. The study was

conducted in compliance with U.S. Good Clinical Practices (21).

Study data management and data analyses were shared by Averion International (Southborough, MA) and StatKing Consulting (Fairfield, OH). Averion performed study monitoring, clinical event committee management, and site auditing, following a prospective statistical analysis plan. Outcomes were evaluated locally and adjudicated by an independent clinical event committee composed of a nephrologist, an infectious disease consultant, and an expert in pharmacovigilance who were not involved in the trial and were blinded to patients' treatment group assignments.

### Study Population

Adult patients with end-stage renal disease older than 18 yrs receiving hemodialysis three times weekly through a cuffed and tunneled internal jugular venous catheter with a mean baseline flow rate  $>300$  mL/min were eligible for participation in the trial if they had no clinical or laboratory evidence of active infection within the preceding 30 days and a negative pre-enrollment blood culture. Patients with femoral and subclavian catheters were excluded, as were patients with catheters with antithrombotic or antimicrobial coatings. Additional exclusion criteria included pregnancy, thrombocytopenia or other chronic coagulopathy, history of heparin-induced thrombocytopenia, antibiotic therapy within 14 days of enrollment (30 days for vancomycin), and hypersensitivity to heparin, sodium citrate, methylene blue, methylparaben, or propylparaben. Written informed consent was obtained before screening and enrollment.

### Randomization

Eligible consenting patients were randomized 1:1 to one of the two treatment groups from computer-generated randomization lists at each site using a permuted block design stratified by dialysis catheter age.

### Intervention and Conduct of the Trial

Study patients were randomized to have each lumen of their hemodialysis catheter locked between dialysis sessions with a solution of sterile saline containing 5000 units of unfractionated heparin (control) or the C-MB-P solution. Before the next dialysis treatment session, the lock solution was removed with a sterile syringe and each lumen was flushed with 5 mL sterile normal saline before connecting the catheter to the dialysis machine tubing.

Individual study center personnel were formally retrained in standardized aseptic technique for hemodialysis catheter care before

the study began, which included the use of masks and sterile gloves for all contact with the patients or their catheters, soaking the catheter hub with gauze impregnated with antiseptic, allowing the catheter to dry on a sterile field before accessing it, and exit site care, which included cleansing of the site with antiseptic and application of a new sterile dressing after each dialysis (3).

At each dialysis session, study patients were evaluated for fever and other signs suggestive of infection. Blood cultures, exit site cultures if there was purulence at the exit site, and other studies, as indicated, were obtained whenever study patients had fever or chills, unexplained hypotension, or other clinical signs or symptoms suggestive of systemic infection (3).

### Definitions

**CRBSI.** Definite CRBSI was defined as fever (temperature  $>38^{\circ}\text{C}$ ) with concordant positive blood cultures drawn from the catheter and a peripheral vein or a peripheral blood culture and a concordant exit site culture. Concordant CRBSI was defined as two concordant positive blood cultures but with temperature not exceeding  $38.0^{\circ}\text{C}$ . Probable CRBSI was defined as fever with one positive blood culture. In each category, there was no clinically identifiable source of bloodstream infection other than the catheter.

**Patency Failure.** In clinical practice, blood flow rates and inflow and outflow line pressures are monitored during hemodialysis sessions. Low flows result in reduced efficiency of dialysis. A baseline blood flow rate through the catheter was measured at study entry at a standardized inflow (arterial) line pressure of  $-200$  mm Hg ( $Q_{b-200}$ ). During subsequent dialysis sessions, if nurses were unable to obtain the prescribed blood flow rate and an intervention was planned, then measurement of  $Q_{b-200}$  was repeated. If  $Q_{b-200}$  had decreased by 20% from the baseline, interventions were allowed, such as instillation of a thrombolytic agent or catheter angiography. A decrease of  $Q_{b-200} >20\%$  with failure to restore flow after one to three interventions that culminated in removal of the catheter constituted patency failure.

**Adverse Events.** Adverse events include unanticipated adverse effects, related adverse events, and severe adverse events, as previously defined (22).

### Outcome Measures

**Primary Outcome Measures.** Primary outcome measures are CRBSI, patency failure, and adverse events.

**Secondary Outcome Measures.** Secondary outcome measures are analyses of catheter blood flow rate over the course of the study, death from any cause, and composite end points introduced to address multiple out-

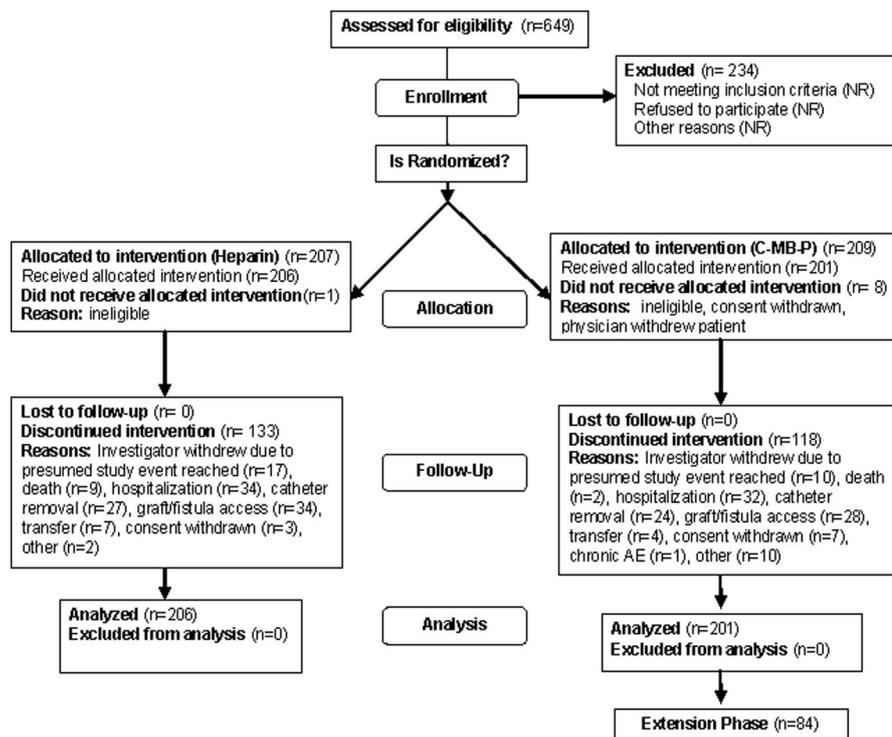


Figure 1. Patients screened, enrolled, randomized, and treated in the trial and included in the final intention-to-treat study analysis. C-MB-P, 0.24 M (7.0%) sodium citrate, 0.05% methylene blue, 0.15% methylparaben, and 0.015% propylparaben; NR, not reported.

comes and to control type I error associated with multiple testing for overall treatment effect, combining catheter-related BSI, patency failure, adverse events, and death from any cause. Patients with more than one primary end point in these analyses were counted only once.

## Statistical Methods

Study sample size was based on an analysis of the weighted overall incidence of CRBSI in 20 recent published studies, which formed the basis for projecting an incidence of CRBSI in the control group of 3.1 per 1000 catheter days. We calculated that approximately 400 patients would need to be enrolled to provide an 80% power to detect a 40% reduction in the incidence of CRBSI in the C-MB-P group with a 5% type I error.

All randomized patients who received any treatment were included in the statistical analyses (intention-to-treat principle). A two-sided Fisher's exact test was used to compare the two treatment groups for dichotomous baseline characteristics, CRBSIs, patency failures, adverse events, and deaths (StatXact version 7; CyTel, Cambridge MA). A singly-ordered exact two-sided Kruskal-Wallis test was used to compare the overall distributions of CRBSI outcomes for the two study groups and as a gatekeeper test for justifying analyses of aggregated CRBSI outcomes. The cumulative risk of CRBSI developing in the two treat-

ment groups during the first 26 wks after randomization was compared by a log rank test on the Kaplan-Meier estimates. A two-sided Fisher's exact test was used to compare incidence rates (ignoring event timing); an exact one-sided lower confidence bound was computed for the heparin and C-MB-P groups for noninferiority testing. Unpaired *t* test was used to compare continuous baseline characteristics of the study population, the mean baseline, end-of-study catheter blood flow rates, and the mean number of thrombolytic or radiologic mechanical patency-restoring interventions needed per patient.

## RESULTS

### Enrollment

Of 650 potential candidates screened (Fig. 1), 416 patients were randomized but nine were never treated because they were found to be ineligible or withdrew; 407 patients (heparin, 206; C-MB-P, 201) were treated and studied for a total of 49,565 (heparin, 24,395; C-MB-P, 25,274) catheter days (Fig. 1).

### Baseline Characteristics of Study Patients

Patients in the two study groups were very similar demographically and in

terms of factors influencing the risk of CRBSI: comorbidities, nutritional status, previous CRBSI, length of time on hemodialysis, and age of the catheter (Table 1, Fig. 2). Patients in the control heparin group were studied for an average of 118 days (52 dialysis sessions) and 126 days (55 sessions) in the C-MB-P group.

### Catheter-Related BSIs

As shown in Table 2, there were 20 CRBSIs—six definite, six concordant, and eight probable—in the control heparin group and six CRBSIs—three definite, one concordant, and two probable—in the C-MB-P group (9.7 vs. 3.0 infections per 100 catheters; 0.82 vs. 0.24 infections per 1000 catheter days; relative risk, 0.29; 95% confidence interval, 0.11–0.70; *p* = .005). No patient had more than one CRBSI. The gatekeeper analysis of the overall distribution of CRBSIs in the three categories was also highly significant (Kruskal-Wallis test, *p* = .004). Reductions in CRBSI in the C-MB-P group were seen with BSIs caused by coagulase-negative staphylococci, Gram-negative bacilli, and enterococci and streptococci (Table 3). Survival analysis of the cumulative risk of CRBSI in the two treatment groups by log rank test (Fig. 2) showed the C-MB-P lock solution provided total protection against CRBSI for the first 10 wks and high-level protection for the entirety of the study period (*p* = .0016).

### Preservation of Catheter Patency

The mean baseline catheter blood flow rates at study entry were 349 and 345 mL/min in the two treatment groups (Table 4, *p* = .53). The mean proportion of dialysis sessions with the flow rate >80% of baseline flow rate and not requiring an intervention to restore patency was 85.2% for the control heparin group and 83.6% for the C-MB-P group (*p* = .38). There were no significant differences in the gradual decline in flow rate over the course of the study in the two groups. Four catheters were lost because of patency failure in the control group and none was lost in the C-MB-P group (*p* = .04 by log rank test).

### Adverse Effects and Deaths

Three patients in the C-MB-P group experienced a device-related adverse event, transient dysgeusia in two cases

Table 1. Characteristics of patients in the two treatment groups

Parameter	Treatment Group		p
	Control	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, 0.015% Propylparaben	
N patients/catheters	206	201	
N catheter days, mean ± SD	118.4 ± 60.5	125.7 ± 62.6	.2307
General health and risk factors at outset:			
Age, yrs, mean ± SD	61.7 ± 15.2	62.2 ± 15.4	.7279
Male, n (%)	51.5	48.8	.5860
Ethnicity/race, n (%)			.4250
White	68.9	67.7	
Black	25.2	28.9	
Other	5.2	3.5	
End-stage renal disease			.867
Diabetic nephropathy	48.5	46.8	
Nephrosclerosis	10.1	12.4	
Glomerulonephritis	4.4	5.0	
Polycystic kidney disease	3.4	2.5	
Other	33.5	33.0	
Blood pressure, baseline, mm Hg, mean ± SD			
Systolic	149 ± 28	148 ± 29	.7767
Diastolic	78.0 ± 19.1	78.1 ± 17.7	.9332
Hypertension	11.7	11.4	1.00
Mean albumin, g/L, mean ± SD	3.82 ± 0.45	3.74 ± 0.41	.0946
Age of catheter, mo, mean ± SD	2.6 ± 6.2	2.6 ± 6.3	1.0000
Type of catheter, n (%)			.8512
Single body, split tip	93 (45.1%)	97 (48.3%)	
Single body, nonsplit tip	80 (38.8%)	74 (36.8%)	
Twin venous and arterial	32 (15.5%)	30 (14.9%)	
Not reported	1 (0.5%)	0 (0%)	

and transient diarrhea in one case (Table 5). Six patients in the control group had a severe adverse event: three had severe sepsis, two had major hemorrhage, and one had interdialytic hypotension. Three patients in the C-MB-P group had a severe adverse event: one had pulmonary embolism, one had myocardial infarction, and one had unexplained high fever without sepsis. Five patients in the control group had severe sepsis as contrasted with none in the C-MB-P group ( $p = .06$ ).

Nine patients in the control heparin group died during the trial, two with septic shock and one with intracranial hemorrhage; two died in the C-MB-P group, one with pneumonia and the other of cardiac causes ( $p = .06$ ).

### Composite Outcome Measures

As shown in Table 6, comparisons of composite outcome measures that encompass CRBSI, catheter patency, and adverse events, including death from any cause, showed robust superiority of the C-MB-P lock solution over heparin.

### DISCUSSION

Infection is the second leading cause of death in patients with end-stage renal disease, with bacteremic sepsis as the cause of 75% of infectious deaths (4). Death rates from sepsis in patients on hemodialysis are 100-fold greater than those of the population at large (23). Patients dialyzed through catheters are two- to three-times more likely to be hospitalized for infection and to die of sepsis than dialysis patients with grafts or fistulas (3, 14, 15). Although the federal government and the National Kidney Foundation have made major efforts to reduce the use of catheters for maintenance hemodialysis but because of unresolved barriers, the proportion of patients dialyzed through catheters has not declined materially in recent years (5). Thus, there is an urgent need to develop more effective strategies to protect hemodialysis patients from CRBSI and loss of access from catheter thrombosis.

Measures for prevention of CRBSI are most likely to be effective if they are based on a sound understanding of pathogenesis (18). With short-term noncuffed central venous catheters, microorganisms from the patient's skin around the insertion site that gain access extraluminally or intraluminally are the source of most catheter-related BSIs (18, 24). Over

The difference between the two groups is highly significant ( $P=0.0016$  by log-rank test).

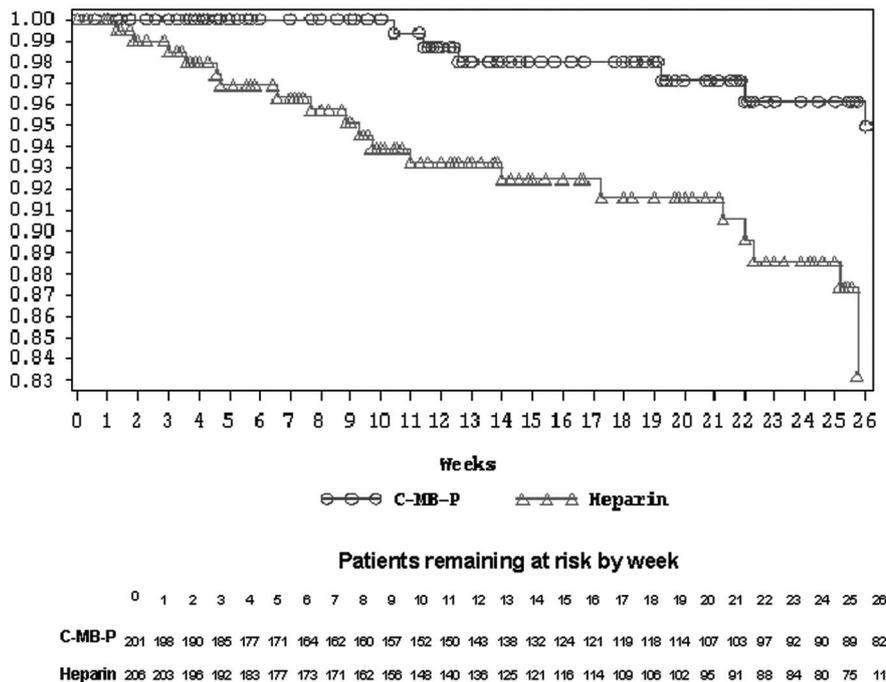


Figure 2. Kaplan-Meier estimates of the cumulative likelihood of freedom from catheter-related bloodstream infection in the two treatment groups. C-MB-P, 0.24 M (7.0%) sodium citrate, 0.05% methylene blue, 0.15% methylparaben, and 0.015% propylparaben.

Table 2. Outcome of catheter-related bloodstream infections

Outcome	Treatment Group		Relative Risk (95% Confidence Interval)	p
	Controls (206/24,395) <sup>a</sup>	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, and 0.015% Propylparaben (201/25,274) <sup>a</sup>		
N CRBSI				
Definite	6	3		
Concordant	6	1		
Probable	8	2		
Total	20	6		
CRBSI per 100 patients	9.7	3.0	0.33 (0.14–0.77)	.007
CRBSI per 1000 catheter days	0.82	0.24	0.29 (0.12–0.70)	.005

CRBSI, catheter-related bloodstream infection.

<sup>a</sup>N study catheters/n catheter days.

Table 3. Microbiology of catheter-related bloodstream infections

Catheter-Related Bloodstream Infection	Treatment Group	
	Controls	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, and 0.015% Propylparaben
<i>Staphylococcus aureus</i>	9	5
Coagulase-negative staphylococci	4	
Gram-negative bacilli	4	1
Enterococci or streptococci	3	

Table 4. Outcome of catheter patency

Outcome	Treatment Group		p
	Controls	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, and 0.015% Propylparaben	
Entry BFR, mean ± SD	348.6 ± 54.1	344.8 ± 65.3	.5263
BFR over trial, mean ± SD	358.6 ± 41.7	355.5 ± 40.4	.4564
BFR slope over study, mean ± SD	0.19 ± 2.71	0.25 ± 5.55	.3069
Tissue plasminogen activator interventions (n dialysis sessions)	67	97	.3303
Patency failure with catheter loss (n)	4	0	.1233

BFR, baseline flow rate.

the past decade, U.S. hospitals that have taken a highly organized systems approach, which starts with formal training of personnel who insert and care for central venous catheters and focuses on limiting femoral vein insertions, use of maximal sterile barriers during catheter insertion, disinfecting insertion sites with tincture of chlorhexidine rather than iodine-based antiseptics, and promptly removing unneeded catheters, have reported striking reductions in the incidence of central venous catheter-

associated BSI within their intensive care units (25, 26).

With long-term intravascular devices, including permanent cuffed and tunneled central venous catheters, most CRBSIs derive from microorganisms that have gained access to the catheter lumen during use of the device (17, 18). Basic infection control with hemodialysis catheters relies on the use of maximal sterile barriers at insertion and sterile barriers and chlorhexidine disinfection when accessing the catheter

and performing insertion site care, and a high level of consistency has been associated with a lower risk of CRBSI (3). Nonetheless, realizing that the rates of CRBSI reported in recent trials with permanent hemodialysis catheters have ranged between two and five per 1000 catheter days (3, 12, 13), there is clearly a role for innovative technologies designed to prevent microorganisms from colonizing the implanted catheter, negating the impact of poor aseptic technique or unique patient vulnerability (18).

The antimicrobial catheter lock is an innovative technique of local prophylaxis in which an anti-infective solution is instilled into the catheter lumen and allowed to dwell for a proscribed period of time, in the case of hemodialysis catheters, for the 2- to 3-day interval between dialysis sessions. In maintenance hemodialysis, a variety of anti-infective solutions have been evaluated in comparative trials (10–13), nearly all of which have been in single centers, including the antibiotics vancomycin, gentamicin, cefotaxime, and minocycline, each with heparin; taurilidine in combination with citrate; ethylenediaminetetraacetic acid, alone or in combination with antibiotics; citrate, alone or in combination with an antibiotic or taurilidine; and ethanol with heparin. Four recent meta-analyses of the individual prospective, randomized, controlled trials published since 1997 each found a significant reduction in the overall incidence of CRBSI, with a pooled risk reduction in the range of 0.30–0.40 (10–13). None of the individual trials found any evidence that the use of anti-infective lock solutions promoted antimicrobial resistance. However, 8 months after a large outpatient hemodialysis program adopted routine gentamicin-heparin lock prophylaxis for 1488 patients dialyzed in eight units, CRBSIs caused by Gram-positive organisms resistant to gentamicin, primarily coagulase-negative staphylococci and enterococci, were encountered; 34 infections were ultimately identified over 3 yrs, prompting discontinuation of gentamicin lock prophylaxis (27). A hemodialysis program in New Zealand also recently reported a modest increase in gentamicin resistance of coagulase-negative staphylococci recovered from CRBSIs after adopting gentamicin locks (28). It seems clear that anti-infective lock solutions with activity against multiresistant Gram-positive and Gram-negative bacteria as well as fungi,

Table 5. Outcome of adverse effects

Outcome	Treatment Group			p
	Controls	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, and 0.015% Propylparaben	Relative Risk (95% Confidence Interval)	
All-cause death (n)	9	2	0.22 (0.03–1.09)	.0621
Adverse events (n)				
Related	0	3	0 (0.42–1.00)	.1195
Severe	6	3	0.51 (0.08–2.38)	.5032

Table 6. Outcome of composite variables

Outcome	Treatment Group			p
	Controls	0.24 M (7.0%) Sodium Citrate, 0.05% Methylene Blue, 0.15% Methylparaben, and 0.015% Propylparaben	Relative Risk (95% Confidence Interval)	
CRBSI or patency loss	24	6	0.23 (0.08–0.60)	.0010
CRBSI or death	29	8	0.26 (0.10–0.61)	.0007
CRBSI, patency loss, or death	33	8	0.23 (0.09–0.51)	.0001

CRBSI, catheter-related bloodstream infection.

but that will not promote antimicrobial resistance, are needed. The novel product that we have studied, C-MB-P, is an antiseptic rather than an antibiotic and is unlikely to select for CRBSIs caused by resistant microorganisms or to promote resistance to systemic antimicrobials used clinically.

Prevention of catheter loss from intraluminal thrombosis poses the other major challenge to stable vascular access in hemodialysis. Dialysis centers routinely lock both lumens of the catheter with an anticoagulant solution at the conclusion of each dialysis session. Whereas citrate is commonly used in Europe, heparin is used most widely in U.S. centers, in concentrations ranging from 1000 to 10,000 units/mL (29). Even when the volume of lock solution is matched to the volume of the lumen, a substantial amount leaks into the systemic circulation (30), and prolonged partial thromboplastin times can persist for up to 4 hrs (31). The use of heparin in the hemodialysis catheter lock solution has been linked to a significantly increased risk of bleeding, especially in children (6, 7, 31). Heparin-induced thrombocytopenia, which in its full-blown type II form is associated with devastating thromboembolic complications, occurs in 0.5%–4% of patients on maintenance hemodialysis when heparin is used in the lock solution

(8, 9). Furthermore, heparin antibodies, which are now detectable in many chronic hemodialysis patients, have been linked to increased cardiovascular mortality (32, 33). In 2008, heparin manufactured in China was implicated in thousands of cases of illness and hundreds of deaths around the world because of toxic concentrations of oversulfated chondroitin sulfate in the final product (34). Finally, there is evidence that heparin promotes biofilm formation (35). It seems clear that antithrombotic strategies other than heparin are needed to preserve the patency of hemodialysis catheters.

Moderate concentrations of citrate in a lock solution, in the range of 4%–10%, have been shown to provide protection against patency failure of permanent hemodialysis catheters comparable to heparin in comparative trials (36–38); however, these concentrations have weak antibacterial activity and do not offer protection against infection. Much higher concentrations of citrate, in the range of 30%, have antibacterial activity, are active against bacterial biofilms (35), and have been shown in randomized clinical trials to reduce the risk of CRBSI (39). However, these concentrations cause a rapid egress of lock solution from the catheter because of high density of the citrate, and these concentrations of citrate have been linked to fatal cardiac

arrhythmias (40) and are unlikely to gain approval from the Food and Drug Administration (41).

The novel lock solution we have studied and report, C-MB-P, offers an antithrombotic alternative to heparin and protection against CRBSI. In the largest, prospective, randomized, controlled trial to examine the utility of an alternative antithrombotic and an anti-infective lock solution in 407 patients studied for an aggregate of 50,000 catheter days, we found C-MB-P to be as effective as heparin in preserving catheter patency; none of 201 catheters followed for a mean of 150 days was lost because of patency failure (Table 4). Furthermore, despite a surprisingly low rate of CRBSI in the control group, a tribute to the quality of infection-control practice in the study centers, patients in the C-MB-P group had a 71% reduction in CRBSI (Table 2 and Fig. 2), with protection against all major groups of bacterial pathogens (Table 3). The solution was at least as safe as heparin and showed a strong trend toward reduced all-cause mortality in the trial (Table 5). Comparisons of composite outcome measures combining CRBSI, catheter patency, and adverse outcome events, including death from any cause, also showed superiority of the C-MB-P lock solution (Table 6). Only 15 patients (95% confidence interval, 9–55) would need to be treated to prevent one CRBSI.

This study has several limitations, most notably the inability to mask patients' lock group assignment because of the deep blue color of the C-MB-P solution. However, the primary study end points, CRBSI and loss of catheter patency, are unlikely to be vulnerable to subconscious bias in a nonblinded trial. Furthermore, clinicians in the individual study centers were unaware of the aggregate outcomes during the trial, and the members of the clinical event committee assessing outcomes were blinded to patients' treatment group assignments. Second, the baseline incidence of CRBSI during the trial was much lower than expected, based on reported rates in recent published trials, and we believe this was partly because of the retraining in aseptic technique and basic infection control practices provided to the personnel in each study center before the study started. Nonetheless, the study still had adequate power to rigorously establish the capacity of the C-MB-P solution to provide substantial protection against CRBSI as well as patency failure.

We believe that the evidence is clear: C-MB-P with a moderate concentration of citrate provides protection against thrombosis comparable to heparin. Furthermore, lock solutions with anti-infective activity can substantially reduce the risk of CRBSI in maintenance hemodialysis, even in centers with a low baseline rate, and warrant consideration for routine use.

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## APPENDIX

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