

# Minocycline-EDTA Lock Solution Prevents Catheter-Related Bacteremia in Hemodialysis

Rodrigo Peixoto Campos,<sup>\*§</sup> Marcelo Mazza do Nascimento,<sup>†</sup> Domingos Candiota Chula,<sup>‡</sup> and Miguel Carlos Riella<sup>\*†</sup>

<sup>\*</sup>Center for Health and Biological Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil; <sup>†</sup>Division of Nephrology, Hospital Universitário Evangélico de Curitiba, Curitiba, Brazil; <sup>‡</sup>Clínica de Doenças Renais do Novo Mundo, Curitiba, Brazil; <sup>§</sup>Division of Nephrology, Hospital São Lucas, Campo Largo, Brazil

## ABSTRACT

There is growing concern about the development of antibacterial resistance with the use of antibiotics in catheter lock solutions. The use of an antibiotic that is not usually used to treat other serious infections may be an alternative that may reduce the clinical impact should resistance develop. We conducted a randomized controlled trial to compare a solution of minocycline and EDTA with the conventional unfractionated heparin for the prevention of catheter-related bacteremia in hemodialysis patients during a period of 90 d. The study included 204 incident catheters (27.8% tunneled); 14 catheters were excluded because of early dysfunction and 3 because of protocol violations. We observed catheter-related bacteremia in 19 patients in the heparin group (4.3 per 1000 catheter-days) and in 5 patients in the minocycline-EDTA group (1.1 per 1000 catheter-days;  $P = 0.005$ ). We did not detect a significant difference in the rate of catheter removal for dysfunction. Catheter-related bacteremia-free survival was significantly higher in the minocycline-EDTA group than in the heparin group ( $P = 0.005$ ). In conclusion, a minocycline-EDTA catheter lock solution is effective in the prevention of catheter-related bacteremia in hemodialysis patients.

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Despite all efforts to reduce the use of catheters in hemodialysis units because of related complications, the frequency of catheter use continues to rise, probably in consequence of the tendency to place native arteriovenous fistula at all cost.<sup>1,2</sup> The main complications related to catheter use are dysfunction (inadequate blood flow) and infection. The type of infections comprise *exit-site infection*, *tunnel infection*, and *bacteremia*. Despite the fact that exit-site and tunnel infections are the most common complications,<sup>3,4</sup> catheter-related bacteremia (CRB) is the most serious one, representing a barrier to long-term catheter use and emerging as a significant cause of morbidity and mortality.<sup>5</sup> Some studies have demonstrated that in patients using a hemodialysis catheter, the risk of death is 1.5- to threefold higher when compared with patients with a primary arteriovenous fistula.<sup>5–7</sup> Moreover, in a large cohort, the occurrence of septicemia was asso-

ciated subsequently with higher cardiovascular morbidity and mortality.<sup>8</sup> A recent clinical trial addressing the prevention of CRB demonstrated that 12% of bacteremia-episodes resulted in death.<sup>9</sup> For these reasons, the prevention of CRB has become one of the major challenges in the routine care of hemodialysis patients.

In recent years several studies have employed specific locking solutions instead of the usual hep-

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**Correspondence:** Rodrigo Peixoto Campos, Center for Health and Biological Sciences, Pontifícia Universidade Católica do Paraná, Rua Imaculada Conceição, 1155, CEP 80215-901, Curitiba - PR, Brazil. Phone/Fax: +55 41 32712285; E-mail: [rodrigopcamos@uol.com.br](mailto:rodrigopcamos@uol.com.br)

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arin lock. This resulted in a significant reduction in the rate of CRB.<sup>9–15</sup> Such locking solutions must have both antimicrobial and anticoagulant properties. They are generally a combination of an antibiotic or an antimicrobial substance (taurolidine), on the one hand, and an anticoagulant (heparin, citrate or EDTA), on the other hand. Some investigators used solutions containing only citrate in high concentrations (30% or even 46.7%) because of their antibacterial effect *in vitro*. Recently, five meta-analyses found that antimicrobial catheter locks significantly reduced CRB events (overall risk ratio less than 0.5).<sup>16–20</sup> Despite definite evidence of the benefit of antimicrobial catheter locks, there is no consensus about their routine use. The 2009 Clinical Practice Guidelines concerning catheter-related infections from the Infectious Disease Society of America did not specifically address the issues of prevention of CRB and the use of antimicrobial catheter lock in hemodialysis patients.<sup>21</sup> The recent position statement by the European Renal Best Practice (ERBP) on hemodialysis catheters is the first one to recommend preventive use of an antimicrobial catheter lock to reduce the rate of CRB.<sup>22</sup> The reason why, in previous guidelines on vascular access, antimicrobial catheter locks were not recommended is the fact that, in the past, the majority of antimicrobial catheter locks contained antibiotics, which are routinely used for the treatment of CRB, thus promoting the emergence of resistant bacteria. Recent publications demonstrated the emergence of gentamicin-resistant bacteremia in hemodialysis patients treated with gentamicin-based locks.<sup>23,24</sup> One way to solve this problem is the use of nonantibiotic antimicrobial catheter locks, for example, high concentrations of citrate and taurolidine. The downside is that citrate at high concentrations may cause hypocalcemia, predisposing to arrhythmia and cardiac arrest. Therefore, citrate concentrations in the range of 30% to 46.7% have been considered unsafe.<sup>25</sup> Unfortunately, low concentrations (4%) apparently fail to reduce CRB.<sup>26</sup> Moreover, in a recent double-blind randomized controlled trial taurolidine plus citrate failed to reduce the occurrence of bacteremia and increased the need of thrombolytic treatment because of catheter malfunction.<sup>27</sup>

We reasoned that it would be rational to use an antibiotic in catheter locks that is not indicated for the treatment of systemic infections. Minocycline in combination with EDTA (M-EDTA) is highly effective in eradicating *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans* when these microorganisms are embedded in the biofilm covering catheter surfaces.<sup>28</sup> Furthermore, in a rabbit model, this combination reduced catheter-related bacteremia.<sup>29</sup> The advantage of EDTA is that its anticoagulant activity is at least equivalent to that of heparin. It also eradicates biofilms and has broad-spectrum activity against both gram-positive and gram-negative organisms enclosed in biofilms generated *in vivo*.<sup>30</sup> Two randomized studies in hemodialysis patients were carried out with this solution. The first one demonstrated a reduction in catheter colonization but not in CRB. The study was underpowered, however, and only one event occurred.<sup>31</sup> The other study was performed in prevalent tunneled catheters; M-EDTA eff-

ectively reduced CRB as compared with heparin. The results were similar to those seen with a catheter lock containing gentamicin plus citrate.<sup>13</sup>

The above considerations prompted us to conduct a multicenter, randomized, open-label, controlled trial comparing M-EDTA with heparin as an interdialytic catheter lock. Both untunneled and tunneled incident hemodialysis catheters were assessed. The underlying hypothesis was that M-EDTA solution was associated with less episodes of catheter-related bacteremia and with increased bacteremia-free catheter survival.

## RESULTS

### Characteristics of the Patients and Catheters

In the three centers involved in the study, 516 catheters were implanted from March 2008 to July 2009; 210 catheters fulfilled the inclusion criteria. Nevertheless, during this period, 6 catheters could not be enrolled because of nonpatient consent. The sample of 204 catheters included 150 patients. Seventeen catheters were excluded, 14 because of early dysfunction and 3 because of protocol violation. Ninety-two catheters were followed in the M-EDTA group and 95 in the heparin group (Figure 1).

The two groups were well matched with respect to all relevant baseline characteristics: age, serum albumin, hemoglobin, body mass index, presence of diabetes, catheter type, vein punctured, catheter insertion technique (new vein puncture *versus* over-the-wire; Table 1).

### Catheter-related Bacteremia and Dysfunction

During the period of 90 d, a total of 8748 catheter-days were analyzed (4371 catheter days in the M-EDTA group and 4376 catheter days in the heparin group). The incidence of CRB was significantly lower in the M-EDTA group ( $P = 0.003$ ). CRB occurred in 19 catheters of the heparin group and in 5 catheters of the M-EDTA group. The CRB rates were 4.3 per 1000 catheter-days in the heparin group and 1.1 per 1000 catheter-days in the M-EDTA group ( $P = 0.005$ ; Table 2). Patients with nontunneled catheters had a lower incidence of CRB when locked with M-EDTA (2

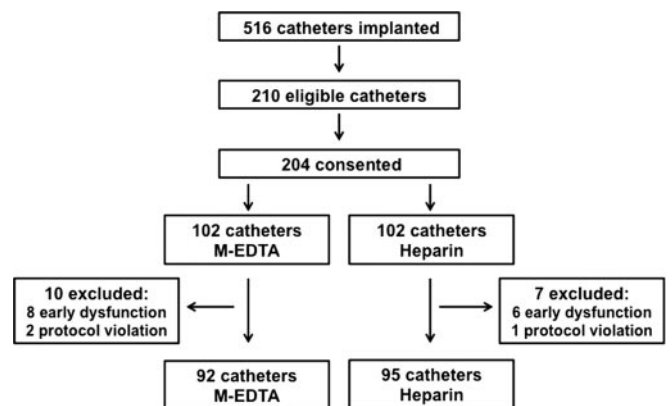


Figure 1. Randomization and follow-up.

**Table 1.** Clinical parameters and catheter data

Parameters	M-EDTA (n = 92)	Heparin (n = 95)	P Value
Age (years)	54.56 ± 16.86	55.55 ± 15.35	0.67
Hemoglobin (mg/dl)	10.04 ± 1.85	10.06 ± 1.75	0.91
Albumin (g/dl)	3.71 ± 0.61	3.69 ± 0.68	0.86
BMI	23.77 ± 4.78	24.23 ± 4.86	0.52
Male gender (%)	62.0	53.7	0.25
Diabetes (%)	35.9	40.0	0.56
Catheter type			0.85
Nontunneled (%)	72.8	71.6	
Tunneled (%)	27.2	28.4	
Insertion technique			0.29
New vein puncture (%)	67.4	60.0	
Change over-the-wire (%)	32.6	40.0	
Location			0.46
Jugular (%)	93.5	90.5	
Subclavian (%)	6.5	9.5	

Values are expressed as mean ± SD. BMI, body mass index.

events) versus those locked with heparin (12 events;  $P = 0.005$ ). This corresponded to 0.7 CRB per 1000 catheter-days for M-EDTA nontunneled catheters versus 4.1 for heparin nontunneled catheters ( $P = 0.01$ ). Although less CRB events occurred in patients with M-EDTA-tunneled catheters (3 events, 1.8 per 1000 catheter-days) compared with heparin-tunneled catheters (7 events, 4.8 per 1000 catheter-days), there was no significant difference ( $P = 0.13$ ). There were 8 episodes of exit-site infection in the M-EDTA group and 9 in the heparin group. One patient from the M-EDTA group and 2 from the heparin group developed tunnel infection. The microorganisms causing CRB are displayed in Table 3. There were no deaths related to CRB. Nevertheless, one patient in the heparin group developed endocarditis and subsequently required valve replacement.

**Table 2.** Catheter-related bacteremia (CRB) and dysfunction

Events	M-EDTA	Heparin	P Value
CRB incidence	5	19	0.003
CRB per 1000 catheter-days	1.1	4.3	0.005
CRB-free survival by day 90 (%)	91.3%	69.3%	
Mean CRB-free survival (days)	85.5	74.9	
Dysfunction incidence	20	14	0.21
Dysfunction per 1000 catheter-days	4.6	3.2	0.31

**Table 3.** Microorganisms isolated in CRB

Microorganisms (count)	M-EDTA	Heparin
Coagulase negative Staphylococcus	3	3
Staphylococcus aureus	2	5
Escherichia coli	—	3
Enterobacter aerogenes	—	3
Klebsiella pneumoniae	—	1
Enterococcus sp	—	1
Pseudomonas aeruginosa	—	1
Proteus mirabilis	—	1
Stenotrophomonas maltophilia	—	1

Twenty catheters had to be removed because of catheter dysfunction in the M-EDTA group versus 14 in the heparin group. The rates were 4.6 per 1000 catheter-days for M-EDTA-filled catheters and 3.2 per 1000 catheter-days for heparin-filled catheters ( $P = 0.31$ ).

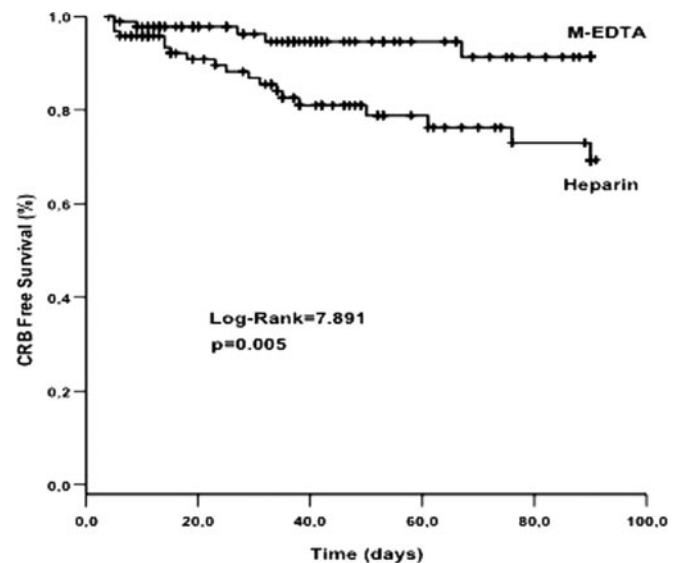
### Catheter Survival Analysis

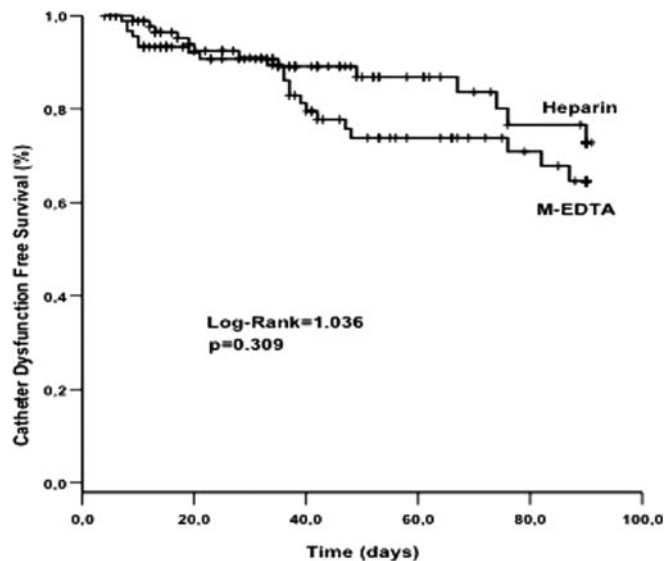
CRB-free survival was significantly higher in the M-EDTA group than in the heparin group (hazard ratio 0.32; 95% CI 0.14 to 0.71;  $P = 0.005$ ). The 90-d CRB-free survival was 91.3% in the M-EDTA group and 69.3% in the heparin group (Figure 2). Nontunneled M-EDTA catheters were associated with a higher CRB-free survival as compared with nontunneled heparin catheters (hazard ratio 0.25; 95% CI 0.09 to 0.72;  $P = 0.01$ ). Nevertheless, tunneled M-EDTA catheters were not associated with significantly superior CRB-free survival (hazard ratio 0.39; 95% CI 0.11 to 1.34;  $P = 0.13$ ).

Catheter dysfunction-free survival in M-EDTA treated catheters did not differ significantly from the heparin group (hazard ratio 1.42; 95% CI 0.72 to 2.78;  $P = 0.309$ ; Figure 3). Similarly, the composite catheter-related bacteremia and dysfunction-free survival were not significantly different between groups (hazard ratio 0.76; 95% CI 0.45 to 1.28;  $P = 0.303$ ; Figure 4).

## DISCUSSION

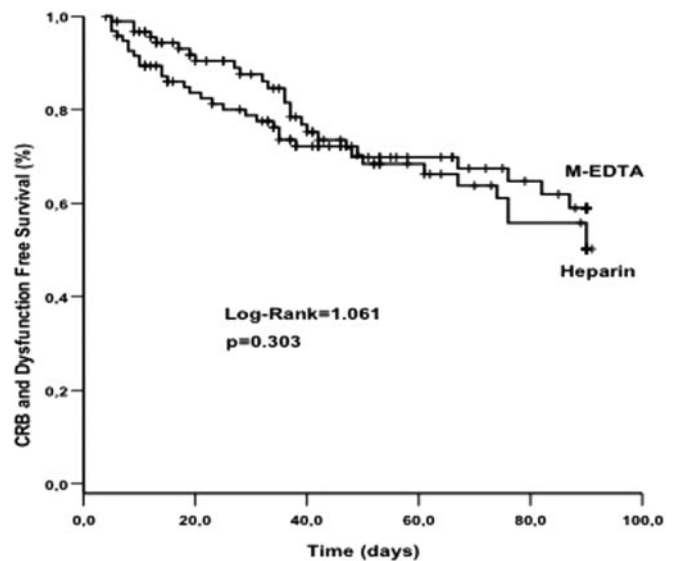
The results of this study demonstrate that an antimicrobial lock solution containing minocycline and EDTA reduces the

**Figure 2.** Kaplan-Meier analysis of the probability that patients would remain free of catheter-related bacteremia (CRB) for all catheters.



**Figure 3.** Kaplan-Meier analysis of the probability that patients would remain free of catheter-related dysfunction for all catheters.

rate of catheter-related bacteremia. This solution reduces the rate of catheter removal because of bacteremia; consequently, it provides a more extended period for the maturation of an arteriovenous fistula without the need to place a new catheter; this was true even in patients with nontunneled catheters. It is important to point out that a reduction in episodes of CRB implies less hospitalization, less cost, less morbidity, and less mortality.<sup>32</sup> Previous studies using antimicrobial catheter locks for both types of catheter had demonstrated a significant reduction of CRB.<sup>9–15</sup> In a well-designed study of trisodium citrate 30% (291 catheters, 66.3% nontunneled), this antimicrobial solution reduced the risk of CRB episodes by 75%.<sup>9</sup> In our study this reduction achieved nearly 73%; this finding documents equivalent efficacy of M-EDTA and trisodium citrate 30%. As mentioned above, five systematic meta-analyses documented the efficacy of antimicrobial catheter locks to prevent CRB.<sup>16–20</sup> Nevertheless, their long-term use is problematic because of the risk of microbial resistance to the antibiotics employed. Some antimicrobial catheter locks contain antibiotics routinely used for CRB treatment, thus predisposing to bacterial resistance. Recently, two studies demonstrated the emergence of gentamicin-resistant bacteremia in hemodialysis patients using gentamicin-based locks.<sup>23,24</sup> The advantage of our solution is that minocycline is routinely used only to treat acne. The concentration of minocycline in this solution represents a minimum inhibitory concentration that is 1500 times higher than that necessary to treat methicillin-resistant *Staphylococcus aureus* infections.<sup>33</sup> Another advantage of this solution is the fact that the association of EDTA improves antistaphylococcus action and adds antifungal action. In addition, it disrupts the structure of the biofilm adhering to catheter surfaces, thus permitting the antibiotic to penetrate and interact directly with germs embedded in the biofilm.<sup>28,30</sup> Despite this greater potential against mainly gram-positive bacteria, the solution may



**Figure 4.** Kaplan-Meier analysis of the probability that patients would remain free of catheter-related bacteremia and dysfunction for all catheters.

have an effect on gram-negative bacteria as well, since no such microorganisms were found in the M-EDTA group compared with eight isolates in the heparin group. Two recent randomized studies using M-EDTA in hemodialysis catheters were reported. The first one did not demonstrate a reduction of CRB.<sup>31</sup> Only 30 catheters were included in each group, however. As a result, only one event occurred. In the present study the rate of colonization was significantly lower in the M-EDTA group compared with heparin (9.1% versus 64.3%). In the study of Nori *et al.*, only tunneled catheters were included.<sup>13</sup> M-EDTA solution (21 catheters) was compared with gentamicin plus citrate (20 catheters) and heparin alone (20 catheters), respectively. Significant reduction of CRB was achieved in the M-EDTA and gentamicin plus citrate groups. There was no difference between these two solutions. In both studies, dysfunction rate, need of thrombolytics, and removal because of catheter thrombosis were not significantly different compared with heparin. This finding demonstrates that effective anticoagulation was achieved with the M-EDTA solution. Despite more dysfunctional events in M-EDTA-treated catheters, rates were not significantly different between groups in our study.

Although an additional analysis showed that tunneled catheters locked with M-EDTA were not associated with significantly longer CRB-free survival, this outcome may be the result of the small sample of tunneled catheters that could be analyzed in the 90-d period. In a *post hoc* analysis at 6 mo of follow-up, the tunneled catheters locked with M-EDTA were associated with a superior CRB-free survival when compared with heparin-tunneled catheters (hazard ratio 0.31; 95% CI 0.10 to 0.98;  $P = 0.046$ ).

It is important to emphasize that our study included only incident catheters. Recently, an observational study with 404 tunneled catheters and more than 135,000 catheter-days found

that the addition of gentamicin to catheters on top of heparin did not significantly reduce CRB. Only catheters locked with gentamicin plus heparin starting at the time of implantation were associated with significant reduction of CRB.<sup>23</sup> This finding may be explained by the fact that heparin alone does not prevent the formation of a biofilm.

One important point is that every reduction of CRB is associated with less antibiotic exposure to patients. There is a rising apprehension about the emergence of *Staphylococcus aureus* resistance to Vancomycin. On the other hand, the prolonged use of gentamicin is associated with the development of hypoaacusia and vestibular symptoms. These two drugs are routinely used to treat CRB in the majority of dialysis facilities because of their better posology in this population. In a *post hoc* analysis, we estimated that the entire number of treatment days for each antibiotic would be 105 d of Vancomycin in the M-EDTA group and 212 d in the heparin group. For gentamicin there were 20 d in the M-EDTA group and 263 d in the heparin group.

The cost of M-EDTA per lock is around US \$4.25, the same as citrate 46.7%. The estimated cost per lock of gentamicin with trisodium citrate (4 mg/ml and 3.13%, respectively) is around US \$2.46, and for gentamicin (5 mg/ml) with heparin, around US \$1.02.

In conclusion, a solution of minocycline with EDTA effectively reduced catheter-related bacteremia in hemodialysis patients during a period of 90 d, thus reducing antibiotic exposure to patients, providing sufficient time for maturation of an arteriovenous fistula created during this period as well as without increased risk of bacteremia and its consequences.

## CONCISE METHODS

### Patient Selection

This study was conducted in Brazil from March 2008 to October 2009. Three dialysis units in the State of Paraná allocated patients to this trial: two units in the city of Curitiba (one in a University Hospital and the other in a dialysis satellite unit) and third one in a Tertiary Hospital in the city of Campo Largo. Only incident tunneled and nontunneled catheters were included in the study. Patients were considered eligible if they were older than 18 yr, had reached end-stage renal disease and required planned hemodialysis by a catheter for at least 2 wk, had no evidence of active infection, and had discontinued any antibiotic at least 7 d before catheter implantation. Only catheters implanted in jugular and subclavian veins were included. Patients fulfilling the inclusion criteria were randomized to the two groups.

Patients were excluded if, in the first two sessions of hemodialysis, the catheter did not allow a pump blood flow rate of >200 ml/min for nontunneled catheters and >250 ml/min for tunneled catheters. Protocol violation was also an exclusion criterion. All catheters were implanted by nephrologists using ultrasound control. The nontunneled catheters were inserted in a procedure room and tunneled catheters in an interventional suite. Each center and operator decided the type (tunneled or nontunneled), model, and length of catheter to be used.

The study adhered to the Declaration of Helsinki and was approved by the local Medical Ethics Committee. Before enrollment, written informed consent was obtained from all patients.

### Study Design

Patients were randomly assigned to filling the catheter in the interdialytic period with either an unfractionated sodium heparin solution (5000 U/ml) or Minocycline with EDTA solution (CATH-SAFE<sup>®</sup>, 3 mg/ml of minocycline and 30 mg/ml of EDTA, Laboratório Lebon, Porto Alegre, Brazil). The M-EDTA solution was prepared by diluting the lyophilized syringe content with 3 ml of isotonic saline. The maximum size of the syringes used was 3 ml. Patients were randomized immediately after catheter implantation and both lumens were locked before leaving the operating room. Randomization was performed by sealed envelope. The investigators were not blinded. After each hemodialysis session, each lumen of the catheter was flushed with 10 ml of isotonic saline solution and locked with the locking solution using a volume exactly equivalent to the internal volume of the lumen of the catheter.

The catheter blood flow and the exit site were evaluated at each hemodialysis session. Catheter data related to blood flow, exit site, and tunnel status were recorded after each hemodialysis session. The catheter exit-site dressing was changed after each dialysis session. Only trained dialysis staff wearing masks and sterile gloves could perform catheter manipulations. Before dressing was applied, the exit site was rinsed with a chlorhexidine-alcohol solution.

### Outcomes and Definition

The primary end point of the study was the occurrence of CRB within 90 d from catheter insertion. The rationale for the selection of this period was the consideration that this time interval provided appropriate time for conversion to an arteriovenous fistula.

CRB was suspicious when a temperature of >37.8 °C, chills, hypotension, mental confusion, or pain occurred. The study protocol required obtaining blood cultures both from peripheral blood and from the catheter. An exit site swab was also collected, if indicated. The criteria to make the diagnosis of bacterial infection was based on the *K/DOQI Clinical Practice Guidelines for Vascular Access*.<sup>34</sup> The definition of the outcomes were based on the *Recommendations of Centers for Disease Control and Prevention (CDC)*, as follow:

1. *Definite blood stream infection*: defined as detection of the same organism by a semiquantitative culture of the catheter tip (>15 colony-forming units per catheter segment) and by a peripheral and catheter blood sample in a symptomatic patient with no other apparent source of infection.
2. *Probable blood stream infection*: defined as defervescence after removal of catheter in a setting where blood cultures confirmed infection but catheter tip did not, or, conversely, where the catheter tip sample confirmed infection but blood cultures did not in a symptomatic patient with no other apparent source of infection.
3. *Possible blood stream infection*: defined as defervescence after removal of the catheter in the absence of laboratory confirmation of blood stream infection in a symptomatic patient with no other apparent source of infection. We decided not to include "possible" blood

stream infection, defined as clinical pointers in the absence of laboratory confirmation of blood stream infection.

Although exit-site and tunnel infections were not a part of the endpoint, they were evaluated and diagnosed using K/DOQI criteria.

After diagnosis, management of CRB was the responsibility of individual physicians and was not specified in the study protocol. If the catheter was removed as part of CRB management, the catheter tip was cultured to further assist in categorizing CRB.

For the purposes of this study, CRB-free survival was defined as the number of days from catheter insertion to diagnosis of CRB as defined above. Exit from the study for any non-CRB cause was treated as a censored observation for the purposes of survival analysis.

*Catheter dysfunction* was defined as the need for catheter removal because, during hemodialysis, a pump blood flow >200 ml/min for nontunneled catheters and >250 ml/min for tunneled catheters was not achieved. In the participating units, the protocol for catheter dysfunction recommended catheter change over-the-wire as the primary step instead of use of thrombolytic agents.

### Statistical Analysis

A retrospective analysis in the hemodialysis units involved in this study demonstrated, in 2007, a CRB rate of 5.5 episodes per 1000 catheter-days. The proportion of patients with CRB-free survival for 90 d was 0.55. Based on this survival rate, we calculated that a sample size of 102 catheters for each group was necessary to achieve a 20% absolute increase in CRB-free survival in the M-EDTA group, for an  $\alpha$  of 0.05 and for 80% power, assuming an early exclusion of 10% of enrolled patients in each group. All analyses were performed on an intention-to-treat basis. Statistical analysis was performed using SPSS software (version 13.0; SPSS Inc., Chicago, IL). Data are shown as mean  $\pm$  SD, as median, or as percentages. CRB and catheter dysfunction rates (events during 1000 catheter-days) were compared using the log-rank test. A comparison between the two groups was performed using the *t*-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. The analysis of categorical variables was performed using contingency tables. CRB and dysfunction-free survivals were analyzed using the Kaplan-Meier method and log-rank test. A *p*-value of less than 0.05 was accepted as significant.

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### DISCLOSURES

None.

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- See related editorial, "Antimicrobial Catheter Locks: Searching for the Ideal Solution," on pages 1781–1782.