AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Successful Salvage of Central Venous Catheters in Patients with Catheter-Related or Central Line-Associated Bloodstream Infections by Using a Catheter Lock Solution Consisting of Minocycline, EDTA, and 25% Ethanol

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In cancer patients with long-term central venous catheters (CVC), removal and reinsertion of a new CVC at a different site might be difficult because of the unavailability of accessible vascular sites. *In vitro* and animal studies showed that a minocycline-EDTA-ethanol (M-EDTA-EtOH) lock solution may eradicate microbial organisms in biofilms, hence enabling the treatment of central line-associated bloodstream infections (CLABSI) while retaining the catheter *in situ*. Between April 2013 and July 2014, we enrolled 30 patients with CLABSI in a prospective study and compared them to a historical group of 60 patients with CLABSI who had their CVC removed and a new CVC inserted. Each catheter lumen was locked with an M-EDTA-EtOH solution for 2 h administered once daily, for a total of 7 doses. Patients who received locks had clinical characteristics that were comparable to those of the control group. The times to fever resolution and microbiological eradication were similar in the two groups. Patients with the lock intervention received a shorter duration of systemic antibiotic therapy than that of the control patients (median, 11 days versus 16 days, respectively; $P < 0.0001$), and they were able to retain their CVCs for a median of 74 days after the onset of bacteremia. The M-EDTA-EtOH lock was associated with a significantly decreased rate of mechanical and infectious complications compared to that of the CVC removal/reinsertion group, who received a longer duration of systemic antimicrobial therapy. (This study has been registered at ClinicalTrials.gov under registration no. NCT01539343.)

Long-term central venous catheters have become a lifeline for patients with cancer, those undergoing transplant, or long-term hemodialysis patients. More than five million central venous catheters (CVCs) are inserted annually in the United States, resulting in approximately 400,000 episodes of central line-associated bloodstream infections (CLABSI) and catheter-related bloodstream infections (CRBSI) (1, 2), each associated with an attributable mortality of 12 to 35% (3, 4) and an attributable cost of $34,508 to $56,000 per episode (5). For CLABSI/CRBSI associated with long-term CVCs (including cuffed/tunneled CVCs or ports with a dwell time of >30 days), the lumen of the catheter is the major source of colonization and subsequent bacteremia (6).

The conventional standard of care in the management of CLABSI/CRBSI involves removal of the infected CVC and replacement with a new catheter at a different vascular site (7). However, in cancer, transplant, and hemodialysis patients with long-term catheters, removal of the CVC and reinsertion of a new catheter at a different site might be difficult or even impossible because of the unavailability of accessible vascular sites. Furthermore, these seriously ill patients with CLABSI/CRBSI and sepsis often have underlying thrombocytopenia or coagulopathy, which would make reinsertion of a new CVC at a different site risky given these comorbidities and related mechanical complications, such as bleeding, hemopneumothorax, misplacement, or arterial puncture (8–12). Furthermore, catheter retention in patients with CLABSI/CRBSI without the use of effective antimicrobial locks is associated with a higher risk of relapse and poor response to antimicrobial therapy (13–15).

In vitro, animal and clinical studies conducted by our group showed that an antimicrobial lock therapy (ALT) consisting of minocycline and a chelator (such as EDTA) may eradicate microbial organisms embedded in a biofilm on the catheter surface, hence enabling the treatment of CLABSI/CRBSI with systemic antimicrobials while retaining the infected catheter *in situ* (16–21). Based on our prior studies, we have learned that adding 25% ethanol to this minocycline-EDTA (M-EDTA) combination enhances its activity and results in an even more rapid eradication of organisms in biofilms, hence reducing the required lock time from 8 to 12 h for M-EDTA alone to 2 h with the addition of the 25% ethanol (22, 23). This will allow for the practical use of the lock in with CLABSI/CRBSI, during which the central line is in high demand and cannot be locked for a prolonged time.

The previous clinical studies that demonstrated the efficacy of the M-EDTA lock (without ethanol) concentrated on the prevention of CLABSI in both hemodialysis and cancer patients (20, 21). There was one anecdotal study that involved three patients in

Received 22 October 2015 **Returned for modification** 7 December 2015
Accepted 14 March 2016

Accepted manuscript posted online 21 March 2016

Citation Raad I, Chaftari A-M, Zakhour R, Jordan M, Al Hamal Z, Jiang Y, Yousif A, Garoge K, Mulanovich V, Viola GM, Kanj S, Pravinkumar E, Rosenblatt J, Hachem R. 2016. Successful salvage of central venous catheters in patients with catheter-related or central line-associated bloodstream infections by using a catheter lock solution consisting of minocycline, EDTA, and 25% ethanol. Antimicrob Agents Chemother 60:3426–3432. doi:10.1128/AAC.02565-15.

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whom M-EDTA alone (without 25% ethanol) was used to salvage the catheter in the setting of CLABSI (24).

This current phase II pilot study (ClinicalTrials.gov registration no. NCT01539343) was designed to assess the efficacy of the triple combination of 1 mg/ml minocycline and 30 mg/ml EDTA in 25% ethanol, the minocycline lock therapy (MLT), for salvaging catheters in the setting of CLABSI/CRBSI, thereby allowing the successful treatment of CLABSI/CRBSI without removal of the CVC.

MATERIALS AND METHODS

Patient population. Between April 2013 and July 2014, we enrolled 30 patients with CLABSI/CRBSI in a prospective, open-label, and single-institution pilot study at The University of Texas MD Anderson Cancer Center (MDACC) in Houston, TX.

Eligible patients were age ≥18 years with an indwelling CVC that had been in place for at least 14 days, who were diagnosed with CLABSI, as defined by the Centers for Disease Control and Prevention (CDC) (25). To confirm that the CVC was the source of bacteremia in the patients with neutropenia, we used the Infectious Diseases Society of America (IDSA) definitions for CRBSI as outlined below in "Definitions" (7).

Patients were ineligible if they had any of the following: allergy to tetracycline or disodium EDTA; received disulfiram; severe sepsis; septic shock; prosthetic valve; signs of metastatic deep-seated infection, such as osteomyelitis, septic pulmonary infarcts, endocarditis, or septic thrombosis; tunnel or catheter exit site infection or infusion port pocket abscess, as manifested by purulence at the exit site, inflammation with erythema, or induration of >1 cm in diameter; or *Candida* line infection.

Intervention. After signing the informed consent, these subjects had their CVCs locked with a novel solution containing the triple combination of minocycline and EDTA in 25% ethanol, the minocycline lock therapy (MLT). Each catheter lumen was filled with a volume of 0.8 to 1 ml of MLT solution for 2 h administered once daily, for a total of 7 doses. We preferentially locked all the lumens at the same time. However, if this was not feasible, lumens were locked subsequently at different times.

After 2 h, the lock solution was aspirated, and the catheter lumen was flushed with 10 ml of normal saline.

The first five doses of the lock solution were given sequentially once daily for the first 5 days. The last two doses were given over the following 2 weeks.

The lock solution was prepared by the pharmacy and refrigerated for use within 72 h.

These patients were compared to 60 other historical concurrent control patients with CLABSI/CRBSI who had their CVC removed and had a new CVC inserted. The control group was identified by retrospectively screening the infection control surveillance database at our institution during the same period of enrollment of our prospectively enrolled patients. The control group patients were matched with the cases in a 2:1 ratio based on similar underlying disease (hematologic malignancy versus solid tumor), type of organism, and neutropenic status.

In addition to CVC management, all patients received systemic antibiotics, as per standard of care, based on the IDSA guidelines for the diagnosis and management of intravascular catheter-related infection. As per the design of the study, the systemic management of the infection was left to the discretion of the primary team.

Follow-up and outcome. All enrolled subjects were monitored very closely, at baseline, within 24 h of intervention, during treatment, at the end of treatment (EOT), and at 1 month following the last dose of lock solution. Subjects were followed clinically for the development of any adverse events.

The primary composite outcome was to estimate and assess the adverse events (AEs) leading to the discontinuation of MLT and complications (mechanical or infectious) associated with MLT or with removal and reinsertion of a new CVC. Symptoms related to the lock procedures were evaluated within 24 h after the instillation of MLT. Malfunctioning CVCs resulting in complete occlusion of lumen, inability to withdraw blood and/or infuse fluids through CVC, or rupture of the CVC that led to CVC removal were also considered adverse events.

Potential mechanical complications in the CVC removal/reinsertion group included pneumothorax, hemothorax, bleeding, inability to insert a CVC at a different vascular site within 1 month of CVC removal even though a CVC was required, and other mechanical morbidities.

The composite outcome also included the resolution of CLABSI/CRBSI. This was assessed by microbiological and clinical resolution of the bacteremia within 72 h after the initiation of lock therapy or CVC removal, the absence of deep-seated infections (such as septic thrombosis or endocarditis), and relapse of the infection or infection-related mortality during the follow-up period

This study was approved by The MD Anderson Cancer Center's institutional review board.

Definitions. CLABSI was defined as per the CDC criteria (25). The CLABSI definition was used in nonneutropenic patients. Patients with bacteremia who had no apparent source for their bacteremia except the CVC were considered to have a CLABSI if they had at least 1 positive blood culture with a recognized pathogen or 2 positive blood cultures with a common skin contaminant in the presence of clinical manifestations of infection.

CRBSI was defined according to the current IDSA criteria as a bloodstream infection that fulfills one of two criteria: (i) the same organism is cultured from two simultaneous paired quantitative blood cultures drawn from the CVC and peripheral vein with a CVC/peripheral colony count ratio of ≥3:1, or (ii) a differential time to positivity of at least 2 h, in which blood cultures drawn from the CVC turn positive at least 2 h earlier than the blood culture simultaneously drawn from the peripheral site (7). The CRBSI definition was used in patients with neutropenia.

Neutropenia was defined as an absolute neutrophil count (ANC) of <500 cells/mm^3.

Statistical analysis. χ^2 or Fisher's exact test was used to compare categorical variables, as appropriate. Continuous variables were compared using the Wilcoxon rank sum test, owing to deviation of the data from a normal distribution. All tests were two-sided, and statistical significance was set at a P value of ≤0.05. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

During the study period, 30 patients with CLABSI/CRBSI were prospectively enrolled to receive the lock solution in an attempt to salvage their CVC. Of these patients, 19 (63%) who were neutropenic fulfilled the IDSA criteria for CLABSI/CRBSI (Table 1). Gram-positive organisms were the causative agent in 53% of the bacteremia cases.

The patients received a median number of 7 doses of MLT given on different days (range, 2 to 7 doses).

Patients who received MLT had clinical characteristics comparable to those of the CVC removal/reinsertion control group in terms of age, gender, type of cancer, degree of neutropenia, type of causative organism, and intensive care unit (ICU) admission (Table 1).

The two groups were also comparable in terms of the type of systemic antibiotic therapy used (Table 2). However, patients receiving the MLT received a shorter duration of systemic antibiotic therapy than that of patients who had their CVC removed (median, 11 days versus 16 days, respectively; $P < 0.0001$) (Table 2). The times to fever resolution and microbiological eradication were similar in the two groups (Table 3). However, MLT was administered after a median duration of 4 days (range, 2 to 9 days) from the date of bacteremia, whereas the CVC was removed after a median duration of 2 days (range, 1 to 8 days) ($P = 0.0002$).

TABLE 1 Characteristics of patients receiving lock solution and their controls

Characteristic[a]	Lock solution group ($n = 30$)	Control group ($n = 60$)	*P* value
Age (median [range]) (yr)	54 (21–74)	56 (22–83)	0.7
Male gender	13 (43)	34 (57)	0.23
Type of cancer			0.29
Hematologic malignancy	21 (70)	48 (80)	
Solid tumor	9 (30)	12 (20)	
Neutropenia			
<500 cells/mm^3	19 (63)	36 (60)	0.76
<1,000 cells/mm^3	20 (67)	37 (62)	0.64
ICU admission during study period	4 (13)	4 (7)	0.43
Fever (>38°C) at onset of bacteremia	19 (63)	45 (75)	0.25
Type of central venous catheter			<0.001
PICC	10 (33)	31 (52)	
Nontunneled	5 (17)	22 (37)	
Tunneled	1 (3)	2 (3)	
PAC	14 (47)	4 (7)	
Dialysis catheter	0	1 (2)	
Bacterial species causing bacteremia[b]			0.98
Staphylococcus aureus	5 (17)	10 (17)	
CoNS	5 (17)	12 (20)	
Streptococcus	4 (13)	8 (13)	
Enterococcus	2 (7)	2 (3)	
E. coli	6 (20)	14 (23)	
E. coli and *Streptococcus*	1 (3)	0	
Klebsiella	1 (3)	2 (3)	
Pseudomonas	3 (10)	6 (10)	
Enterobacter	2 (7)	4 (7)	
Serratia marcescens	1 (3)	2 (3)	

[a] Data are presented as no. (%), unless otherwise specified. PICC, peripherally inserted central catheter; PAC, pulmonary artery catheter; CoNS, coagulase-negative staphylococci.
[b] Some bacteremias were polymicrobial.

In addition, patients receiving MLT were able to retain their CVC for a median duration of 74 days (range, 4 to 240 days) after onset of bacteremia. Nineteen patients were able to retain their CVC beyond the last follow-up period and for up to 240 days from the onset of bacteremia. Three patients had their CVC exchanged over a guide wire, and 8 patients had their CVC removed after a median duration of 17 days after initiation of the lock therapy.

None of the patients receiving MLT developed any infectious complication compared to seven patients in the CVC removal/reinsertion arm, of whom three developed septic thrombophlebi-

TABLE 2 Systemic antibiotic treatment of the bacteremia for patients receiving lock solution and their controls[a]

Systemic antibiotic treatment of bacteremia	Lock solution group ($n = 30$)	Control group ($n = 60$)	*P* value
Anti-Gram positive			
Linezolid	4/17 (24)	12/32 (38)	0.32
Daptomycin	10/17 (59)	21/32 (66)	0.64
Vancomycin	14/17 (82)	21/32 (66)	0.32
Telavancin	0/17 (0)	3/32 (9)	0.54
Anti-Gram negative			
Cefepime or ceftazidime	9/14 (64)	17/28 (61)	0.82
Meropenem or ertapenem	11/14 (79)	19/28 (68)	0.72
Piperacillin-tazobactam	7/14 (50)	8/28 (29)	0.17
Days of systemic antibiotic therapy for CLABSI (median [range])	11 (4–24)	16 (5–89)	0.0001

[a] Data are presented as no. (%) of patients, unless otherwise specified. The denominators represent the numbers of patients infected with Gram-positive organisms and those infected with Gram-negative organisms, as indicated. One lock solution patient had infection with both Gram-positive and Gram-negative organisms.

TABLE 3 Clinical and microbiological responses of patients receiving lock solution and their controls[a]

Response	Lock solution group ($n = 30$)	Control group ($n = 60$)	*P* value
Fever resolution (no./total no. [%])	19/19 (100)	44/45 (98)	>0.99
Days between bacteremia and fever resolution	2 (1–9)	2 (0–14)	0.99
Days between starting intervention and fever resolution for patients with fever resolution after starting intervention (catheter removal or lock therapy)	3 (1–4)	2 (1–13)	0.28
Microbiological parameters (no. [%])	30 (100)	60 (100)	
Days between onset of bacteremia and microbiological eradication	3 (1–10)	3 (1–7)	0.61
Days between onset of bacteremia and catheter removal or exchange	74 (4–240)[b]	2 (1–8)	<0.0001
Days between onset of bacteremia and starting intervention (catheter removal or lock therapy)	4 (2–9)	2 (1–8)	0.0002

[a] Data are presented as the median (range), unless otherwise specified.
[b] In 4 patients, the CVCs were still in place at the time of data analysis.

tis, two developed deep-seated infections, and three relapsed. One patient in the CVC removal/reinsertion arm both developed deep-seated infection and relapsed (Table 4).

Similarly, none of the patients receiving MLT developed any mechanical complication compared to six patients in the CVC removal/reinsertion arm. The mechanical complications included failure of insertion (3 patients) and CVC misplacements (4 patients). One patient had two mechanical complications, which was one unsuccessful insertion attempt and one misplacement (Table 4).

Only one patient receiving the lock intervention may have developed a transient alcohol taste after the first dose of lock therapy that did not recur after the subsequent six doses. There was no other lock therapy-related adverse event reported and none resulting in a discontinuation of lock therapy.

Overall complications that included mechanical and infectious complications were significantly higher in patients who had their CVC removed and reinserted compared to those who received the lock intervention (11 versus 0, respectively; $P = 0.014$) (Table 4).

All-cause mortality was similar in the two arms (Table 5). Three patients in the MLT arm died during the course of the study as a result of their underlying malignancy or complicating medical condition. Five patients died in the control arm, three as a result of their underlying disease, one of cardiac arrest, and the last one of an unknown cause that was presumed to be his refractory acute myeloid leukemia, as the patient was discharged home on supportive care after having failed multiple chemotherapy regimens.

TABLE 4 Infectious and mechanical complications associated with lock intervention versus control

Complication by type (no. [%])	Lock solution group ($n = 30$)	Control group ($n = 60$)	*P* value
Infectious			
Patients	0 (0)	7 (12)[a]	0.09
Episodes	0 (0)	8 (13)[a]	
Septic thrombophlebitis	0 (0)	3 (5)	0.55
Deep-seated infection	0 (0)	2 (3)	0.55
Relapse	0 (0)	3 (5)	0.55
Mechanical			
Patients	0 (0)	6 (10)[b]	0.17
Episodes	0 (0)	7 (12)[b]	
Failure of insertion		3/7 (43)	
Misplacement		4/7 (57)	
Overall			
Patients	0 (0)	11 (18)[c]	0.014
Episodes[d]	0 (0)	15 (25)[c]	

[a] One patient had 2 infectious complications, which were deep-seated infection and relapse.
[b] One patient had 2 mechanical complications, which were one failure of insertion and one misplacement.
[c] Two patients each had both infectious and mechanical complications.
[d] Overall complications included infectious complications and mechanical complications.

DISCUSSION

In this phase II pilot open-label study, we have demonstrated that MLT was highly efficacious in salvaging the CVC in the setting of CLABSI/CRBSI, with retention of the CVC occurring for a median of 66 days. The only possible related AE that occurred in a patient receiving MLT was an alcohol taste that lasted 15 s on the first day of lock therapy and was completely uneventful.

The rapid cidal activity of MLT in eradicating resistant organ-

TABLE 5 All-cause mortality associated with lock intervention versus control

All-cause mortality	Lock solution group ($n = 30$)	Control group ($n = 60$)	*P* value
Death within 6 wk after bacteremia	3 (10)	5 (8)	>0.99
Days between bacteremia and death (median [range])	31 (15–31)	34 (20–39)	0.37
Cause of death (no. [%])			
Underlying cancer	3 (10)	3 (5)	
Bacteremia related	0	0	
Multiorgan failure	0	0	
Other cause(s) (cardiac event)	0	1 (2)	
Unknown[a]	0	1 (2)	

[a] Cause of death was most likely related to the refractory acute myeloid leukemia, as the patient was discharged after having failed multiple lines of therapy.

isms in biofilms has been well demonstrated in previous *in vitro* studies and does give biological plausibility to the successful outcome in treating CLABSI/CRBSI without removal of the catheter in this current trial (22, 23). This rapid and highly cidal activity might be multifactorial. The first factor is most likely related to the fact that minocycline has been shown to be more active than linezolid and vancomycin in penetrating and eradicating Gram-positive organisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), in biofilms (26, 27). In addition, EDTA does complement the antimicrobial activity of minocycline in eradicating organisms in biofilms (17, 18). In addition, EDTA was shown to serve as a disruptor of the biofilm matrix through the chelation of iron, calcium, and magnesium, which are essential building blocks of the biofilm extracellular matrix (28). Furthermore, EDTA does serve as an anticoagulant that prevents thrombogenesis and thrombotic occlusions of CVCs (29). Finally, the addition of 25% ethanol has been shown to add to the activity of M-EDTA in rapidly eradicating *Candida* organisms in biofilm and allowing the triple combination to achieve complete eradication of all organisms within a 2-h lock exposure (22, 23).

An M-EDTA lock solution without ethanol was found to prevent catheter-related bacteremia and colonization in clinical trials involving hemodialysis patients and cancer patients (20, 21, 30, 31). However, in all of these preventive clinical trials, the lock time was >24 h. To date, there have been no clinical trials demonstrating the efficacy of M-EDTA in 25% ethanol solution, particularly with a lock time of ≤2 h. The results of this current trial demonstrate that locking the CVCs of 30 patients with documented CLABSI/CRBSI caused by various bacteria resulted in the successful management of this bloodstream infection with systemic antibiotics without any associated mechanical or infectious complications. Compared to a concurrent historical control group with uncomplicated CLABSI/CRBSI, the cumulative risks of both mechanical and infectious complications were significantly higher in the control CVC removal/reinsertion group. It is of note that the Infectious Diseases Society of America (IDSA) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection (7) do recommend CVC removal in most CRBSI. However, a lock solution is recommended as an alternative, particularly when the CVC cannot be removed or when reinsertion is associated with a higher level of complications.

The risk of mechanical complications in this current study was 12%, and the risk of infectious complications was 13%. Since some patients had concurrent infectious and mechanical complications, the overall complication rate was 18%. Several studies have shown that the risk of mechanical complications in critically ill and seriously ill cancer patients associated with reinsertion of a new CVC at different vascular access site approaches a level of 20%. Chaftari et al. (11) estimated the risk of mechanical complications associated with reinsertion of a new CVC after the removal of the culprit CVC in cancer patients with CLABSI to be 15%, with a higher rate of infectious complications in this same patient population. Lennon et al. (12) estimated the overall postprocedural mechanical complication rate associated with 500 CVC insertions to be 19.5%. However, in this study, the risk of mechanical complications dropped substantially if an insertion took place under ultrasound guidance. Reinsertion under ultrasound guidance was used in our study, which also might explain why our risk of mechanical complications was 12%. Based on the results of our current study, the overall significant reduction and protection against mechanical complications and even infectious complications associated with MLT solution do have a great impact, not only on alleviating suffering and morbidity associated with CLABSI/CRBSI, but also on reducing the cost of cancer care and serious illness due to CLABSI/CRBSI.

In addition to all of the above-mentioned factors, what is remarkable in our study is that the MLT solution resulted in a more successful outcome than CVC removal/reinsertion, despite the shorter duration of systemic antibiotic therapy for CLABSI/CRBSI in the MLT group. Also, the improved outcome with MLT was noted even though the time to the initiation of intervention (MLT versus CVC removal) was significantly longer in the MLT group than that in the control group. IDSA guidelines recommend that if an infected CVC is to be retained and an antibiotic lock is to be used, a longer duration of systemic antibiotic therapy would be required (7). Based on results of our study, the reverse seems to be true, in that the duration of systemic antibiotic therapy in the MLT group was shorter than that in the control CVC removal/reinsertion group. This finding of a shorter duration of antibiotic therapy might have major implications in further reducing the cost of care associated with CLABSI/CRBSI.

The AEs associated with the MLT were minimal. The only AE noted was an alcohol taste that lasted for 15 s in one patient during the first therapy. However, this possibly related AE was not reported during subsequent administrations of MLT. It is important to note that in a large study by Slobbe et al. (32), in which a 70% ethanol lock was used in 226 patients, an alcohol taste was reported in 31% of the patients. In addition, the use of 70% ethanol in that same large study was associated with other AEs, such as dizziness/drowsiness in 41% and facial flushing in 39%.

Although our study involved a small number of patients, the low intensity and frequency of reported AEs make this lock solution a very promising one, particularly in view of the improved outcome associated with MLT. However, the use of an antimicrobial lock in the treatment of CLABSI has not consistently been successful (16, 33–36). Vancomycin alone or in combination with heparin was associated with a major failure against CLABSI caused by *S. aureus* (16, 34). Hence, it is important to choose a highly effective antimicrobial lock combination of antimicrobials that penetrate biofilm (such as minocycline) with chelators and a low concentration of ethanol in order to achieve an improved outcome without CVC removal.

The choice of low-concentration ethanol (25%) (32, 37) as a component of the lock intervention in the current study is based on the following rationale: first, the use of 70% ethanol alone was associated with a significantly higher rate of AEs compared to that of the placebo. Second, the use of ethanol concentrations >28% has been associated with plasma protein precipitation (38). Third, ethanol concentrations of ≥60% have been reported to cause mechanical damage to the integrity of the polymer (39). Finally, in animal models and in clinical settings, the use of ethanol alone as a lock solution at a concentration of 50 to 70% has not been associated with successful management of CLABSI (32, 40). There are several limitations to this study. First, this is a single-center study with limited number of patients enrolled in the MLT arm. Second, the retrospective nature of the concurrent control, and the fact that this study was not randomized, might allow an element of bias. Third, this study did not have enough power to show a significant difference in mechanical complications. Taking into account all these limiting factors, our group plans to conduct a large

prospective randomized multicenter study that would be properly powered to show significance in the endpoints achieved.

In conclusion, this study showed that a catheter lock solution consisting of minocycline-EDTA–25%vEtOH is highly effective in salvaging CVCs in patients with CLABSI/CRBSI. In addition, this intervention, compared to the conventional approach of CVC removal and reinsertion, was shown to result in a significantly decreased rate of mechanical and infectious complications. This improvement was noted despite the fact that the MLT group received a shorter duration of appropriate systemic antimicrobial therapy than that of the control group. A large phase III prospective randomized trial is necessary to demonstrate the efficacy of MLT intervention in salvaging CVCs and to decrease the risk of complications associated with CLABSI/CRBSI.

ACKNOWLEDGMENTS

I. Raad is a coinventor of the minocycline-EDTA-ethanol lock solution technology, which is owned by the University of Texas MD Anderson Cancer Center (UTMDACC) and has been licensed to Novel Anti-Infective Technologies, LLC, of which UTMDACC, I. Raad, and J. Rosenblatt are shareholders.

FUNDING INFORMATION

This work, including the efforts of Issam I. Raad and Joel Rosenblatt, was funded by Novel Anti-Infective Technologies, LLC. This work, including the efforts of Issam I. Raad and Joel Rosenblatt, was funded by Leonard-Meron Biosciences.

This work was partly funded by internal funds from the Department of Infectious Diseases and Novel Anti-Infective Technologies, LLC, which has sublicensed the technology to Leonard-Meron Biosciences, Inc., for whom I. Raad is a scientific advisor and shareholder. J. Rosenblatt is a consultant.

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